A STUDY OF SPONGE AS A DISINTEGRATING AGENT IN COMPRESSED TABLETS

By

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INTRODUCTION

Tablets, as a means of administering medicine, have been in existence for over one hundred years. Today, compressed tablets are the most popular form of medication. Americans consume about forty-two million tablets daily (1). Whether or not these forty-two million tablets exert the intended therapeutic action depends to a great extent on one essential property of the tablets, namely disintegration. Despite the importance of this property, it took eighty years from the time tablets were first manufactured in the United States, in 1870, and thirty-four years after the first tablet appeared in the U. S. P. IX, until official requirements for disintegration were established. During the interim, great objection was made to tablets due to the fact that many tablets, as described by one observer, would pass through the human system showing as much change as a glass marble (2).

In order to accomplish tablet disintegration, at least in the case of insoluble materials, it is necessary to add a substance to the tablet formula which has the capacity to break the tablet apart. This agent is called a disintegrator. While there are many conditions which influence the rate of disintegration, the proportions and types of binding and disintegrating agents in the tablet formula are, in many cases, the most important factors controlling the disintegration of this form of medication.

On the basis of a study by Gross and Becker (3), powdered sponge

was found to be the best disintegrating agent among the twenty-two different materials tried. Since their work was limited to lactose tablets and a single percentage of sponge, it was the purpose of this investigation to make a more detailed study of this agent.

Sponges, both natural and synthetic, in varying concentrations were evaluated as disintegrants for compressed tablets. These tablets were compared for disintegration time against tablets containing corn starch as the disintegrator. In addition, the effects of various lubricants and binding agents on disintegration time of the tablets were studied.

REVIEW OF THE LITERATURE

Methods of Preparing Tablets

Tablets are unit dosage forms of medication in the form of a granular powder, with or without diluents, compressed into a suitable shape (4).

The general method of preparing compressed tablets encompasses one of three specific procedures.

a. Direct compression

b. Slugging process

c. Wet granulation process

If the material to be compressed is free-flowing and cohesive without the addition of binders or lubricants, then the first of the above methods, direct compression, is utilized. In this method the material need only be reduced to the proper particle size, which is dependent upon the size of the tablet to be made, and is run directly into the tablet press without any further preparation or special handling.

Some materials, on the other hand, do not possess either cohesiveness or lubricity and these properties must be given to the materials by either one or the other methods of granulation.

The basic objective in granulation is the conversion of the powdered ingredients into a free-flowing, uniformly compressible material. Such a granular material is essential since the compression machines rely on volumetric gravity fill to achieve uniformity in dosage. Upon

completion of the granulation process, the granules must be self binding and non-sticking to the punches and dies (5).

The choice of the granulation method to be used is dependent upon the properties of the materials to be compressed. If the powders are either heat or moisture labile, then the precompression or "slugging" method is used which excludes these two factors from the process. If, on the other hand, these factors are of no concern to the particular formulation in question, one may use the wet granulation process, currently the most widely used method for the preparation of granules for tablet compression.

The process of precompression involves the production of "slugs" or large tablets which are subsequently screened and recompressed into finished tablets. In this method, the ingredients in the formula, which are usually in powder form, are weighed out, mixed, and then sifted through a No. 30 or 40 sieve. The resultant mixture is compressed in heavy duty machines into over-sized tablets called "slugs" which are 3/4" - 7/8" in diameter. These "slugs" are then broken down into appropriate particle size by passing through mechanical granulators with the desired sieves attached (6).

Although the precompression process completely eliminates many steps, which are essential in the wet granulation method, it also possesses several drawbacks. First, the tablets produced are not as hard as those prepared by wet granulation. Secondly, in order to accomplish this method satisfactorily, a slow, heavy duty tablet press is required so that extremely high pressures may be obtained, since such pressures

are necessary for the production of "slugs". A third and most important drawback is the fact that few materials lend themselves to tableting by this method (10).

For materials that cannot be directly compressed, or are not heat or moisture labile, the wet granulation method is perhaps the most generally employed. Here, the material is first converted into a doughy mass through the use of a granulating agent which is capable of aggregating the powders through either a bonding or solvent action on the components of the tablets. This doughy mass is broken up into coarse granules which are subjected to uniform drying. These primary granules are obtained by forcing the aggregated mass through a No. 6 or No. 8 sieve. After these coarse granules have been sufficiently dried, they are further broken down to appropriate dimensions. The size of these final granules has a direct relationship to the appearance and properties of the finished tablet. Malpass (7) stipulated that the mesh size must be governed by the size of the tablet and the hardness desired. In 1947, Silver and Clarkson (11) presented the following schedule of sieve sizes through which the material should be passed for granulation:

Tablet Size	Size Sieve
up to 3/16"	No. 20
7/32" - 5/16"	No. 16
11/32" - 13/32"	No. 14
7/16" and over	No. 12

It is necessary when preparing these final granules, that they

be free from excessive "fines" (8). Little and Mitchell (5) state that fine powders are apt to pack or "bridge" in the hopper, feed shoe, or die; and thus tablets of uniform weight and uniform compression are not obtainable. Nevertheless, it should be kept in mind, that in order to obtain a good tablet a certain percentage of "fines" are necessary. Silver and Clarkson (11) state that 10 - 20 per cent of "fines" based on total granulation are necessary to fill the void space between granules in order to produce a tablet of smooth appearance. Caspari and Kelly (4) advocate the use of 10 - 15 per cent "fines" for optimum tablet appearance. Villacorta (9), working on granulation of acetylsalicylic acid, recommends that "fines", designated as particles less than 125 microns, should not exceed 20 per cent in the granulation mixture.

Contrary to all the above findings, Chavkin (10) states that up to 80 per cent of material finer than 80 mesh (177 microns) can be incorporated into a tablet granulation without adverse effect upon the hardness of the resulting tablet.

The final step in the wet granulation process, before feeding the hopper with the granulation, is lubrication of the granules. Lubrication is accomplished by adding a substance to the dry granulation that will facilitate ejection of the finished tablet from the die after compression.

The disintegrating agent, in some cases, is completely added with the lubricant during addition of the latter to the granules, but in most cases it is mixed with the active ingredient and filler, and an additional amount is very often added to the lubricant.

After addition of these latter agents and proper mixing of the granulation, the material is then ready for compressing.

Disintegrating Agents

An examination of the literature to determine previous research accomplished on disintegrating agents revealed very little published information in this field. Undoubtedly, a great deal of work has been done, especially by pharmaceutical companies, however, since the manufacture of tablets is an art and the uniqueness of many commercial tablets depends upon the type of disintegrating agent used as well as several other factors, much of this knowledge has been carefully guarded by the industry itself and thus remains unpublished. The information found has been seriously considered in the study of this problem.

A disintegrating agent is a substance which is added to the tablet to help break it apart after administration or to hasten dispersion in water (11).

Disintegrators fall into two main classes. They are: (a) substances which will swell in the presence of sufficient moisture or other suitable media; and (b) the addition of chemically reactive ingredients which when wetted will produce a gas upon reaction and break the tablet. The former of these two classes, that is, those substances that swell in the presence of moisture are, by far, the most widely used agents in tablet manufacture.

Corn starch is one of the oldest and still most commonly used disintegrators in tableting. Starches have a great affinity for water

and through rapid absorption the starch grains swell to many times their normal size. This expansion causes the tablet to disintegrate or break apart quite rapidly. This valuable use of starch was first observed by Charles Killgore, an American, who in 1887 applied for a process patent which was denied on the basis that starches had previously occured in tablets though their value was not recognized (12).

Killgore's patent application, No. 238,375, which was filed May 16, 1887, was in part as follows:

> It is well known that the administration of medicines in the form of compressed tablets or pills, while having many advantages, has been open to disadvantage arising from the slowness with which the same dissolve in the stomach.
>
> The object of my present invention is to form tablets or pills which, while possessing all the advantages of those heretofore employed, are not attended by the disadvantage above referred to; in that when subjected to moisture they rapidly disintegrate. This result I accomplish by mixing with the ordinary ingredients constituting a compressed tablet or pill a percentage of starch which will so change the character of the compressed tablet or pill that the same will not be open to the objection heretofore existing.
>
> The tablet or pill resulting from my invention possesses, as far as I know, all of the qualities of those heretofore made excepting when taken into the stomach it immediately disintegrates.
>
> I claim a compressed tablet or pill containing a substantial percentage of starch, for the purpose of facilitating disintegration, as set forth.

The following notation was made by the Patent Examiner in rejecting the patent application:

> Starch is the most commonly used dividing agent. It enters into pills, tooth powders, baking powders, and toilet powders generally. Such having been compressed, there is neither novelty nor invention in applicant's procedure. The application is rejected.

That Killgore's discovery was quickly used, in secret and without credit to him, is indicated by an interesting controversy between two English manufacturers concerning their newly improved tablets (13).

Dieterich (14) wrote, in 1890, that a simple means for

obtaining disintegration of tablets was merely to add some powdered sugar with the active ingredient. Since this method did not accomplish its purpose in all tablets, he advised the introduction of a substance that swells up in water and gave tragacanth powder as an example. He noted the use of 10 - 25 per cent tragacanth as being sufficient.

Blaschnek (15), in 1909, investigated potato, wheat, corn, rice and maranta starches as disintegrating agents. The results clearly showed a distinct advantage for maranta and potato starches. A point brought out by this investigator was that starch must be nearly anhydrous if the best results are desired.

In 1914, Kebler (16) stated that mixtures of a bicarbonate and an acid when incorporated in a tablet and immersed in water react and give off carbon dioxide, thus mechanically breaking up the tablet. In the same paper he mentioned that although powdered agar-agar and Irish moss had been advocated as disintegrators for compressed tablets they had not been used to any extent.

White (2), in a summary on tablet manufacture, wrote that potato starch was far superior to all other disintegrating agents used up to that time. He stated that the potato starch should be added to the dry granulation immediately before compressing and not during the granulation process. When prepared in this manner the tablets were found to swell and rupture when immersed in water.

American and foreign literature on the subject of tablet disintegration is very scanty from 1923 to 1946, the majority of the reports being focused on the application of starch as a means of facilitating

tablet disintegration (17 - 31). Most of this research, however, is repetitious or contradictory and in many cases hinders rather than helps the inexperienced tablet maker.

Husa (23), in 1928, suggested the classification of tablets into different groups according to the type of disintegration they undergo. He noted that certain tablets dissolve without the aid of a disintegrator and that these tablets were made from soluble chemicals. He proposed that tablets of this nature should be classified as a tablet not requiring the aid of a disintegrating agent.

A review on tablet making (24), in 1931, mentioned the use of pectin as a disintegrant for preparing tablets on a large scale. The experiments carried out with the addition of one per cent pectin to the granulation along with a little rice starch proved to give satisfactory tablets with rapid disintegration rates. It was noted that the addition of pectin to tablet masses in quantities of ten per cent or more is not advisable because a thick layer of mucilage forms around the tablet during the process of disintegration or solution, which, unless vigorous shaking is resorted to, prevents the water from coming into contact with the nucleus of the tablet and retards disintegration.

Potato starch, gelonide, and magnesium peroxide have been compared as disintegrants for tablets (27). Gelonide was prepared by treating a ten per cent aqueous solution of gelatin with a few drops of formaldehyde solution until a glue-like consistency was obtained. It was then forced through a No. 22 screen, dried for several hours at 90° C., and powdered. The disintegrants were added to an acetanilid granulation prepared with ten per cent gelatin solution. Potato starch was found to be superior to the other two disintegrants for acetanilid

tablets.

Milne (32) postulated that methylcellulose would be of value as a binding agent and compared it to other granulating agents by the disintegration time of the resulting tablets. He used the following granulating agents: (a) 10 per cent gelatin solution, (b) 50 per cent alcohol, (c) 10 per cent starch paste, (d) equal parts of mucilage of acacia and syrup, and (e) 3 per cent methylcellulose solution. In all cases, the tablets made were Compound Aspirin Tablets, B. P. C., and all conditions were kept as constant as possible. Milne found that methylcellulose compared favorably with starch paste and gelatin solution, the disintegration in these three cases being of the explosive type. He also indicated that tablets made with alcohol or the acacia mucilage-syrup mixture as a binding agent disintegrated very slowly. Because methylcellulose is stable to heat and is not subject to attack by microorganisms and molds, he suggested its use as a binding and disintegrating agent for compressed tablets.

In 1949, Granberg and Benton (33), working on tablet formulations, stated that bentonite serves both as a filler and disintegrating agent when added to thyroid tablets. Because the color of bentonite is approximately the same as that of powdered thyroid, they suggested its use as being advantageous over starch, since the latter has a tendency to discolor the tablet.

Studying alginic acid as a disintegrating agent, Berry and Ridout (30), found that when ten per cent was added in phenobarbital tablets, it gave a much better disintegration time than 15 per cent of potato starch, and in the case of barbital tablets the time of disintegration was

approximately the same. They stated that alginic acid can be granulated with the medicaments in a tablet which has the following advantages:

a. The addition of a very fine powder, such as starch to the granules before tableting, means that there is a considerable risk of separation of powder and granules during the transfer of the bulk material to the tablet machine and also, whilst the material is in the hopper, due to the vibration of the hopper or of the machine itself. This separation of fine powder will cause variation in weight of the tablets and also variation in the amount of active ingredient in each tablet. There is also the difficulty- by no means inconsiderable- of ensuring an even distribution of a large quantity of starch in a bulk of granules.

b. Since the alginic acid in these experiments is an integral part of the granules, when the tablet breaks up it will do so to give material which is smaller than the original granule. The active constituents thus being presented in a finer form will be more quickly absorbed and give a more rapid therapeutic action.

c. The process of tableting will be simplified.

Gross and Becker (3) discovered two new substances and claimed them to be more effective disintegrating agents than many of those commonly used. These new agents were powdered sponge and dried citrus pulp, both prepared in the laboratory from natural Florida products. These were tested along with 20 other substances on a comparative basis. The agents used were: corn starch, bentonite, and tragacanth, all of U. S. P. XIV grade; pectin, karaya gum, sodium alginate, and methylcellulose (100 and 4000 cps.) all of N. F. IX grade; also Gelloid 50, locust bean gum, algin, Veegum HV, Aveeno, and CMC 70. In a separate category were magnesium peroxide, and combinations of calcium carbonate with either citric acid, pectin, or urea monophosphate, in addition to sodium carbonate peroxide and sodium pyrophosphate peroxide. For the investigation, tablets were prepared without medicament, lactose being used as the inert filler and two per cent leucine as the lubricant.

Two granulating solutions were employed. One contained five per cent Zein (corn protein) in isopropyl alcohol and the other had five per cent zein in a mixture of syrup, water and alcohol. Alternative methods were employed for incorporating the disintegrating agents: (a) the whole of the agent was mixed with the lactose before moistening with the granulating solution; (b) five per cent of the agent was reserved for admixture with the lubricant after granulation. For each test the same amount of disintegrating agent was used, namely, 17 per cent. In order to obtain results of a comparative nature, the disintegration times were extrapolated from individual hardnesses to a hardness of seven kilograms. All hardness tests were determined with a Monsanto Hardness Tester. The authors concluded from this study that powdered sponge not only was the most effective disintegrating agent of the 22 studied but also that tablets prepared with it as the disintegrant remained stable after being aged at room, elevated, and reduced temperatures. No changes in either hardness or disintegration time were noted after 500 hours of aging.

In 1953, Swintosky and Kennon (34) prepared two powdered acid gums, namely, carboxymethylcellulose (CMC acid) and linseed acid. They described a new procedure for the preparation of these acids in a powdered, water dispersible form. A preliminary study using these agents in compressed tablets indicated that carboxymethylcellulose possesses tablet disintegrating properties analogous to those of powdered alginic acid; however, it was suggested that further work be carried out in order to make a true evaluation of these substances for that purpose.

Firouzabadian and Huyck (35), in 1954, compared four substances

with corn starch as disintegrating agents for tablets of both soluble and insoluble medicaments. These substances used in ten per cent concentrations included alginic acid, Veegum HV, methylcellulose, and a starch-agar mixture. Sodium bicarbonate was selected as the soluble medicinal ingredient while aluminum hydroxide served as the ingredient for the insoluble tablets. Of these four agents tested, alginic acid and Veegum HV compared favorably as disintegrants for the particular formula of sodium bicarbonate tablets while the starch-agar mixture and Veegum HV were the best for those tablets containing aluminum hydroxide. Although these latter two substances gave satisfactory disintegration rates when used in the aluminum hydroxide formula, they could not be recommended since in ten per cent quantities they discolored the tablets slightly. The authors, however, did suggest their use as disintegrating agents for colored or coated tablets.

Eatherton, et al., (36) tested three grades of guar gum as disintegrating agents for tablets of digitalis, lactose, sulfathiazole and thyroid with corn starch being used as a control in the disintegration tests. Although one and one-half per cent of each of the three grades of guar gum produced effective disintegration times for the sulfathiazole and lactose tablets, this same concentration of gum had no advantage over corn starch when used in digitalis and thyroid tablets. Following storage tests of increased temperature and humidity, the hardness values of the tablets prepared in this study were found to have decreased from their original values.

In 1955, Swintosky, et al., (37), tested several new powdered polysaccharide acids for their effects on the hardness and disintegration

time of sulfathiazole tablets. Several of these new polysaccharide type acids were shown to hasten disintegration whereas others retarded disintegration. It was found that alginic acid, carboxymethylcellulose in powdered acid form (HCMC), elm acid and starch served to facilitate tablet disintegration, whereas linseed acid, quince acid, arabic acid and plantago acid served as disintegration retarders. The authors, in summarizing, stated that since delayed or sustained drug release have become so popular in recent years, disintegration retarders or inhibitors such as arabic acid, linseed acid and quince acid may possibly be employed when these actions are desired.

The mechanism through which starch serves as a disintegrating agent, from the discovery of its use in 1887 up until recent times, has not been disputed. However, Curlin, in 1955 (38), stated that the disintegration action of starch was not due to its swelling property but instead due to its capillary action in the tablet. This action, he noted, may be due to the spherical shape of the starch which increases the porosity of the tablets. When placing a drop of dye solution on a tablet and then cutting it in two, he found the color had penetrated the tablet as though it were a blotter. To substantiate his claims, he stated that, upon examination of the slurry obtained from disintegrated tablets, the starch granules were not swollen.

Methods of Testing Disintegration

Although the need of a substance to facilitate the breaking up of a compressed tablet had been realized since 1900, it was not until 25 years later that studies were undertaken to find a method which would

give reproducible disintegration rates of tablets. Before this time the disintegration rate of a tablet was noted by dropping it in a glass of water and observing its breakdown.

The methods of determining the disintegration time of tablets fall under two main classes. The first class includes those methods which test for hardness and resistance to breakage and the second includes those methods which test for speed at which the tablet will dissolve or break up into its original granules when placed in a liquid at a specified temperature. Research has thus far produced 27 disintegration methods, of which two fall under the first class and 25 under the second class (39). It is easily realized, after a careful review of these methods, that there is a great amount of confusion as to the value of these disintegration studies and that the many variables arising from them show a definite need for standardization.

Probably the first attempt to study disintegration testing in a systematic manner was carried out in 1930 (40). This was the earliest comprehensive investigation of tablet disintegration and was conducted by a subcommittee of the Research Board of the APMA, under the chairmanship of George Ewe. Ewe described a method for determining disintegration of tablets based on a classification as to where and how the tablet disintegrated or dissolved. Nine classes of tablets were designated as follows:

a. Uncoated tablets intended to disintegrate or dissolve rapidly in the stomach.

b. Uncoated tablets intended to disintegrate or dissolve in the stomach.

c. Hypodermic tablets.

d. Uncoated tablets intended to dissolve or disintegrate in water at room temperature.

e. Uncoated tablets intended to dissolve or disintegrate in water at elevated temperatures.

f. Uncoated tablets intended to pass into the intestines and be disintegrated there.

g. Coated tablets intended to disintegrate rapidly in the stomach.

h. Coated tablets intended to disintegrate in the stomach.

i. Coated tablets intended to pass into the intestines and be disintegrated there.

In addition, Ewe recommended a method of determining the disintegration time of tablets and suggested maximum rates of disintegration for certain classes of tablets.

In 1934, the Swiss Pharmacopoeia gave the first official method for testing disintegration and in 1936 the subject was discussed at the British Pharmaceutical Conference (41).

Brown, in 1939 (27), devised his own method for determining tablet disintegration. He determined the force (weight) required to break tablets when dry and again when wet. The ratio of these two breaking points was taken as the significant measure since it would control the degree of attrition during transport and storage as well as the clinical effectiveness of the tablets.

Also in 1939 Berry (42), upon request of the British Pharmacopoeia Committee, investigated and reported on a new method for determining tablet disintegration. For this method he used a specially constructed wire device, which, when weighted, cut through the tablet. Later this device

was modified by Berry and Smith (43), but it was admitted that while the method contributed to research in the field, it was actually a measure of the rate of softening rather than disintegration. Finally, in 1945, the 7th Addendum to the British Pharmacopoeia was published, introducing a standard test for the disintegration of tablets.

Several articles were published from 1942 to 1945 by both American and British authors containing descriptions and results of tablet disintegration tests (44 - 48).

In 1946, Gershberg and Stoll (49) described the apparatus that has been in use in chemical inspection laboratories of the U. S. Army Medical Department since 1940. This apparatus was noted as having several advantages over other disintegration methods and also as being capable of testing enteric coated tablets, since they could first be immersed in an acid-pepsin solution for a specified period and then transferred to an artificial intestinal fluid without taking the tablets out of the apparatus.

During the year of 1948, the Stoll-Gershberg apparatus was studied by a subcommittee of twelve members. The subcommittee generally agreed, after intense investigation, that it fulfilled the requirements as well as any simple, mechanical apparatus could be expected to do, and recommended its use for a disintegration test to be included in the forthcoming revisions of the U. S. P. and N. F. The recommended test and time limits of official tablets appeared in the U. S. P. XIV and N. F. IX with only slight modifications. However, additional experience on the disintegration of compressed tablets has caused the end-point definition of the official test to be revised in the current U. S. P. and N. F. The

former end-point definition read (50): "the tablets are completely disintegrated when substantially no residue remains on the screen." Since it was found that certain tablets do not break down during this test but instead form soft residues that will easily break down with the slightest touch of a finger or stirring rod, the following new clause was added to the original end-point definition. It now reads (51): "the tablets are disintegrated if substantially no residue remains on the screen or if any residue that remains is a soft mass having no palpably firm core."

Factors Influencing Tablet Disintegration

Since most compressed tablets are composed of more than one ingredient and require several steps in manufacture, it is possible that these factors greatly affect disintegration rates for any given tablet. There is much evidence to show that the following are contributory factors affecting the rate of disintegration:

a. The nature of the active and other constituents used.

b. The type and quantities of binding agents used.

c. The disintegrator used.

d. The lubricant used.

e. The size and weight of the finished tablet.

f. The hardness of the finished tablet.

g. The degree of compression.

h. The speed of compression.

i. The type of hopper feed in the machine, particularly if the disintegrant is added to the finished granules.

j. The age of the tablets.

k. The means of testing disintegration.

Among the substances that will influence the disintegration of the finished tablet are: the active medicament, e. g., which may be organic or inorganic, a salt or an acid, an ester or an alcohol, all of which may have different crystal structure and properties that will influence the compression characteristics of a formula; the binding agent which is usually carbohydrate or proteinaceous in character; the fillers, which, depending on their nature and content have a great influence on the final tablet; the disintegrant; and the lubricant. Combinations of these many substances when compressed will yield a certain structure which may be varied according to the physical properties and particle sizes of the ingredients (52). It is obvious that, as the structure of the tablet it changed, the disintegration rate will be affected.

Several independent studies have indicated the existing relationship between the active ingredient of the tablet and the rate at which the tablet disintegrates (35, 36, 53, 54). Firouzabadian and Huyck (35) have shown that in order to control disintegration, the selection and quantity of disintegrant used in the formula must be made according to the nature of the active ingredient. They reported that the solubility of the finished tablet has a marked effect on the time at which it disintegrates.

Indications of the inhibitory action of binding agents on the disintegration of tablets have been reported by numerous workers (29, 32, 36, 55, 56, 57). Chavkin (10) in discussing problems of producing compressed tablets, indicated the indiscriminate use of binding agents during

the process of granulation as being the cause of excessively hard granules, which invariably, when compressed, result in the production of tablets with prolonged disintegration rates.

According to Strickland, et al., (58) the addition of excessive proportions of lubricant to the granules produces softer tablets with a severalfold increase in disintegration time. The best lubricants were found to be impervious to water (59), making it evident that an excess of such a lubricant will have a waterproofing effect on the finished tablet, thus hindering its disintegration rate. Other recent reports have also described this effect of lubricants on disintegration (60, 61).

Higuchi, et al., (54), in a report on the physics of tablet compression, stated that hardness varied directly with the logarithm of compressional force, leveling off at high forces. It also was found to vary directly with the apparent density of tablets. Using varying proportions of disintegrant in the same basic formula, they found that the logarithm of the disintegration time also varied directly with compressional force, and that higher rates of disintegration were produced by increasing the proportion of disintegrant. In some instances, however, when a high percentage of disintegrating agent was present, faster rates of tablet disintegration were obtained as the maximal compressional force was increased. This continued up to an optimum compression after which the ordinary relationship of disintegration time with compressional force was manifested. These results are in general agreement with those observed by Berry and Ridout (30) who had determined the disintegration times of the different tablets as a function of the ratio of the weight to height of the tablets which they called "compression ratio", and is

obviously the same as maximal force applied during the compression of the tablets.

Statements have been made that the uniformity of tablet mixtures could be modified during compression due to mechanical vibration of the tablet press (30, 62). In general, the disintegrating agent is added in the form of a very fine powder to the granules just previous to tableting; therefore, any separation of powder and granules before or during compression would undoubtedly result in uneven distribution of the disintegrant which would in turn influence disintegration of the finished tablets. Raff (63) described a method of following this separation of fine material by means of statistically recording resultant tablet weights, compressional pressures, hardness, and changes in color, supplemented by a test utilizing sieving at an intermediate point. He reported this separation to be enhanced by starting with a full hopper and operating until the supply of granulation was exhausted; he suggested that the hopper be kept filled to a reasonable level during tableting if this is to be avoided.

The effect of aging on disintegration times of tablets has been the subject of many investigations (1, 29, 30, 36, 64, 65, 66). Because these investigations have been carried out on an independent basis, the data collected is very broad and seems to indicate that the effect of age on tablets cannot be generalized but instead must be determined for the particular tablets in question. However, the reports cited do agree that the factors influencing the effect of age on tablet disintegration are as follows; the conditions of storage, the length of time stored, the containers used for storage, and the nature of the tablets stored.

DeKay and Holstius (31) stated in a recent paper that of all the variables investigated, such as active ingredient, binding agent, disintegrating agent, hardness of tablet, etc., no one variable was solely responsible for influencing the disintegration rate of the finished tablet. They postulated that disintegration is probably due to the interaction of all these factors combined.

Sponge

Tschirch (67) believes the medicinal use of sponges dated back to the Salernian School (13th century). Sponge ash was official in the pharmacopoeias of the 18th and 19th centuries, appearing last in Pharm. Helv. I (1865). As late as 1899, the United States Dispensatory, 18th edition, set up standards and methods of preparation for Spongia officinalis (68).

Besides the specific use for goiter, due to their iodine content, sponges have also been used for surgical procedures, where their great absorptive power is utilized.

Unfortunately, early investigation and classification of sponge was hindered and confused by the fact that it was believed to be plant rather than animal. As late as the middle of the 19th century it was often classified in the plant kingdom, and the animal character of the sponge was definitely established only in the last few years of the century (69).

Due to a lack of broad knowledge of the sponge, the few studies that have been undertaken on it often disagree on many points. For example, even now there is no universally accepted system of naming and

classifying sponges. One of the best documented systems of classification now in use is that of M. W. deLaubenfels (70). This system is comparatively new, but is becoming very popular and widespread.

Sponge in its natural state, when alive, is covered and permeated throughout with a gelatinous substance known as "gurry". Soon after the sponge is collected this "gurry" is removed by washing and expressing. This process of washing and expressing, when finished, leaves but the fibrous skeleton of the animal, and it is in this condition that the sponge is sold on the market.

Stadeler (71), in 1859, was first to give the fibrous skeleton of the sponge a name; he called it "Spongin". Spongin is classified under scleroproteins (albuminoids), which include all proteins having a supporting or protective function in animal organisms (72). More specifically, it belongs to the class of scleroproteins known as keratins. The keratins have been defined as insoluble proteins which are extraordinarily resistant to digestion with the usual proteolytic enzymes. Spongin, according to Block (73), is classified still further as a pseudokeratin, thus being less resistant toward enzymatic hydrolysis than the eukeratins.

The most recent and by far the most complete elemental analysis of spongin was performed by Ramsey in 1948 (74). Three species of Florida salt water sponges furnished the spongin for the analysis. The results of Ramsey's analysis of the sheep's-wool sponge, the same species used in the present investigation, are summarized as follows:

Nitrogen ------	14.68 per cent	Bromine ------	0.53 per cent
Carbon --------	46.04 per cent	Potassium ----	0.36 per cent
Hydrogen ------	6.06 per cent	Iron ---------	0.27 per cent
Oxygen --------	29.71 per cent	Calcium ------	0.52 per cent
Sulphur -------	0.08 per cent	Barium -------	0.14 per cent
Phosphorus ----	Trace	Sodium -------	0.14 per cent
Iodine --------	0.74 per cent	Copper -------	0.05 per cent
Chlorine ------	0.32 per cent	Ash ----------	3.90 per cent

Trace Elements ---- Aluminum, Boron, Chromium, Lead, Manganese, Nickel, Silver, Strontium, Vanadium and Titanium.

The organic nature of spongin from a chemical standpoint has been ascertained as being protein by several workers (73, 75, 76). Studies on the amino acid content of these proteins, however, have been few, and most of those undertaken have neglected to mention the exact specie of sponge used in the analysis. Sheep's-wool sponge obtained from Florida's west coast has been reported by Wintter (77) as being made up of the following amino acids: aspartic acid, glycine, alanine, lysine, arginine, proline, glutamic acid, threonine, tyrosine, hydroxyproline, phenylalanine and leucines (mixture of isomers).

Although no specific studies have been reported on the toxicology of sponge on human subjects, experiments on animals have indicated it to be non-toxic to the species of animals used (78).

EXPERIMENTAL PROCEDURE

Materials and Equipment Used

The materials and equipment used in this investigation are listed in Tables 1 and 2.

TABLE 1

MATERIALS USED

Material	Quality
Sponge	Natural
Sponge	Synthetic
Corn Starch	U. S. P.
Calcium Gluconate	U. S. P.
Sulfadiazine	U. S. P.
Dried Aluminum Hydroxide Gel	U. S. P.
Bismuth Subnitrate	N. F.
Magnesium Hydroxide	N. F.
Bismuth Subcarbonate	U. S. P.
Lactose	U. S. P.
Sodium Bicarbonate	U. S. P.
Syrup	U. S. P.
Zein	Food
PVP (Plasdone)	Commercial
Locust Bean Gum	Food
Magnesium Stearate	U. S. P.
Talcum	U. S. P.
Boric Acid	U. S. P.
Isopropyl Alcohol	N. F.
Potassium Permanganate	U. S. P.
Sodium Bisulfite	U. S. P.
Hydrochloric Acid	U. S. P.
Glycerin	U. S. P.
Sucrose	U. S. P.
Sulfurous Acid	Reagent
Hydrogen Peroxide Solution	U. S. P.
Sodium Perborate	N. F.
Oxalic Acid	Reagent
Sodium Thiosulfate	N. F.

TABLE 2

EQUIPMENT USED

Equipment	Description	Source
Tablet press	Rotary B-2	F. J. Stokes Machine Company
Tablet press	Eureka	F. J. Stokes Machine Company
Mikro-Pulverizer	Bantam	Pulverizing Machinery Company
Comminuting mill	Model D	W. J. Fitzpatrick Company
Wiley mill	Model No. 2	A. H. Thomas Company
Sifter (electric)	Model P-S	Read Standard Corporation
Sieves		
8, 14, 40 mesh	Stainless steel	Newark Wire Cloth Company
10, 20, 40 mesh	Brass	E. H. Sargent Company
60, 80, 100 mesh	Wire cloth	E. H. Sargent Company
200, 350 mesh	Stainless steel	Read Standard Corporation
Dough Mixer	Model K-20	Read Standard Corporation
Ribbon blender	Model 21-AA	F. J. Stokes Machine Company
Air circulating oven	Model 38-B	F. J. Stokes Machine Company
Oven (electric)	Storage	Precision Scientific Company
Analytical balance	Chainomatic	A. S. Aloe Company
Prescription balance	Class A	Torsion Balance Company
Platform scale	Model 4021-Y	Toledo Scale Company
Refrigerator	Frigidaire, 22 ft.^{3}	General Motors Corporation
Disintegration apparatus		J. VanderKamp Instrument Company
Hardness tester		Monsanto Chemical Company
Shaking machine	Model 8918	Fisher Scientific Company
Cenco DeKhotinsky thermostat		Central Scientific Company
Lightnin' mixer	Model F	Mixing Equipment Company, Inc.
Stainless steel tanks	San-I-Tanks	Metal Glass Products Company
Pony mixer	Model 13111	J. H. Day Company, Inc.
Sling psychrometer	ML-24	Signal Corps, U. S. Army

Description of Sponges Used

Natural Sponge

Sheep's-wool sponge was chosen as the source of the spongin because of its availability and commercial importance. The Sheep's-wool sponge, in the form of clippings, was obtained from the commercial sponge markets of Tarpon Springs, Florida.

The classification set forth by M. W. deLaubenfels (70) was followed for the identification of the material used in this study. For Sheep's-wool sponge it is as follows:

Phylum: Porifera
Class: Demospongia
Order: Keratosa
Family: Spongiidae
Genus: Hippiospongia
Species: Hippiospongia lachne

For the sake of convenience, the name, spongin, was frequently used in place of the common name, wool-sponge, or the species name, Hippiospongia lachne.

Synthetic Sponge

The synthetic cellulose sponge was obtained locally in block form and had the dimensions of 4½" x 3" x 1" in length, width, and thickness, respectively. This synthetic sponge was manufactured by E. I. DuPont de Nemours Company, Incorporated.

Treatment of Spongin Before Use

The spongin used in this study was in the form of clippings which were trimmed from sponges in the process of preparing them for market. These clippings, in the state obtained, contained large proportions of sand, shell, and other foreign material. The inclusion of these particles in the organism is a mechanical process which takes place during the growth of the sponge. The particles are not part of the spongin composition since the sponge is non-calcareous and non-siliceous (70). Because of the large amount of foreign material and the dark yellowish-brown color of the sponge, it appeared that a thorough cleaning and decolorization was necessary before it could be used in a tablet formula.

Cleansing Procedure

A batch of about three to four hundred grams of sponge was taken by selecting the cleaner and more perfectly formed pieces. These pieces were inspected and any large foreign particles present were removed by hand picking. The sponge was then placed in a stainless steel tank containing tap water and soaked for a period of twelve hours. During this soaking period the sponge was kneaded and churned by hand periodically. This operation was repeated four or five times depending on the need of the particular batch, each time using a fresh bath of water. After each wash, the spongin was skimmed from the sand and other foreign material which had settled to the bottom of the tank. Fragments that were still heavily contaminated were found on the bottom of the tank with the residual matter. These fragments were discarded along with

the foreign material since they were unsuitable for use. After the last washing period the spongin was pressed to remove the water. Upon examination of this washed sponge, it was found that several minute pieces of calcareous matter still remained embedded. In order to remove these particles a further wash was given using a cold bath of two per cent hydrochloric acid instead of the tap water used in the previous washings. The spongin was allowed to remain in this acidulated bath for twelve hours, after which, upon removal, it no longer showed any traces of calcareous material. The spongin was then thoroughly rinsed in several baths of cold water, pressed by hand to remove excess water, and oven-dried at 140° F. for five hours. Representative samples of the dried sponge were selected, and inspected for foreign matter with a hand magnifying glass. This inspection revealed no sand, shell, or other foreign bodies present in or on the cleansed sponge. The next step, before the grinding process, was to remove the dark yellowish-brown color by a bleaching treatment.

Bleaching Procedure

In search of a method to bleach natural sponge, several bleaching agents were tried with little or no success. The agents tried were aqueous solutions of sodium thiosulfate, sodium hypochlorite, oxalic acid, hydrogen peroxide, and sodium perborate.

Although sulfurous acid showed some promise of good bleaching action on the sponge, the best results were obtained through the use of potassium permanganate followed by a sodium bisulfite treatment.

To decolorize the spongin, the cleansed dried material was placed in a one per cent solution of potassium permanganate for one-half

hour. This procedure was repeated five times, using a fresh solution of potassium permanganate each time. When the sponge was removed from the permanganate bath it was dark brown in color due to a deposit of an oxide of manganese. This colored compound was removed by washing the sponge in a twenty per cent cold solution of sodium bisulfite. The sponge was then placed in a ten per cent sodium bisulfite solution, which had been acidified with hydrochloric acid, for thirty minutes. This last steeping was repeated, using fresh acidified solutions, until the color had been sufficiently bleached. The bleached spongin was then rinsed in several changes of fresh water to remove all residues of chemicals and dried at 145° F. Sponge clippings before and after cleansing and bleaching are shown in Figures 1 and 2.

Figure 1

Sponge clippings before cleansing and bleaching.

Figure 2

Sponge clippings after cleansing and bleaching.

Grinding Procedure

Before the spongin could be incorporated into a tablet formula, it had to be ground to a suitable fineness so that it could be uniformly mixed with the other materials.

Because of the physical nature of the sponge, several experimental runs were undertaken before a suitable method of grinding could be obtained. The use of a Fitzpatrick Comminuter was found to be of little value in grinding the sponge because of its large grinding chamber and also because of the fibrous "bouncy" properties of the sponge. The revolving blades, upon striking the sponge, would cause it to be thrown out of the grinding chamber and back into the feed throat, and as a result, the sponge was ground at a very slow rate. The use of this machine made it necessary to regrind the material several times, each time passing it through a smaller screen, before it was suitable for use. Since this procedure was not feasible, other types of grinders were tried.

It was found that by using a Wiley Mill grinding of the sponge became relatively easy. The Wiley Mill is an attrition type mill having four knives on a revolving shaft that work with a shearing action against six knives which are set in the frame. The shearing action of the cutting edges, between which there is always a clearance, powdered the spongin without difficulty. Two screens, 2-mm. and 1-mm., respectively, were used. These screens dovetail into the frame of the mill so that none of the material comes out of the grinding chamber until it is fine enough to pass through. To facilitate grinding, the bleached sponge was cut up into fragments of about four to eight centimeters in length

before being fed into the hopper of the mill. The second milling was collected and stored in screw-capped, brown bottles at 45° C. for future use in tablet formulas.

Attempts made to size the powdered spongin using standard mesh sieves were unsuccessful. When screening for sizing, portions of the powder would pass through a No. 200 mesh screen, however, when it was collected and resieved through the same screen, all of the same powder would not pass through as it did previously. This was accounted for by the fact that, after the first screening some of the powder would "mat", and upon subsequent sieving through the same screen only that powder which had not matted would go through. Although this powder could not be sized accurately, it was required to pass through a No. 40 mesh screen before being used in a tablet formula.

Treatment of Synthetic Sponge Before Use

The same procedure used for grinding the natural sponge was used for powdering the synthetic sponge. The synthetic sponge required no special treatment before grinding with the exception of cutting the blocks into fragments of about three centimeters in length. Like natural sponge, this also was ground first through the 2-mm. mesh screen and then through the smaller 1-mm. mesh screen. The powder produced after milling through the smaller screen had the appearance of dry sawdust. The powdered synthetic sponge was collected and stored in brown bottles at 45° C. Before using this powder in tablet mixtures it was passed through a No. 40 mesh screen.

Tablet Constituents

Active Ingredients

The medicinal ingredients selected as the active components of the tablets prepared in this study were represented by drugs of variable solubilities. As a control, lactose replaced all of the active medicinal agent in the tablet. The drugs used as active ingredients are described in Table 3.

TABLE 3

DRUGS COMPRESSED INTO TABLETS

Drug	Solubility in Water	Mesh Size
Calcium Gluconate	Sparingly Soluble	20/40
Sulfadiazine	Insoluble	40/60
Dried Aluminum Hydroxide Gel	Insoluble	80/100
Bismuth Subcarbonate	Insoluble	40/60
Bismuth Subnitrate	Practically Insoluble	40/60
Magnesium Hydroxide	Practically Insoluble	100/200
Sodium Bicarbonate	Freely Soluble	40/60
Lactose	Freely Soluble	40/60

Diluent

For those formulas requiring a diluent, Lactose, U. S. P., was used.

Disintegrating Agents

Sponges, both natural and synthetic, were compared with corn starch for their effectiveness as disintegrating agents when used in compressed tablets.

It should be noted here that the addition of disintegrating agent to the formula varied depending on the properties of the agent used and also on the formula being prepared. Husa (79) indicates that some of the disintegrating agent may be mixed with the medicaments prior to granulation while an additional amount may be added to the dry granules before compression. The portion added to the dry granulation before compression serves to disintegrate the tablet into its original granules while that which is mixed with the medicaments prior to granulation serves to break apart the individual granules.

In this investigation some formulas required the disintegrants to be added either before granulation with the active ingredient and filler or to the dry granules prior to compression while in other formulas a combination of both methods was used.

In the case of powdered spongin, its addition to the dry granules just previous to compression had several disadvantages. The chief disadvantage was the inability of the powdered spongin to flow freely with the granulation from the hopper into the die. Instead, it had a tendency to mat up and become unevenly distributed throughout the granulation thus affecting uniform concentration in the finished tablets. Another disadvantage of powdered spongin, when added to the granulation in this manner, was that at times it "bridged" the bore of the die which in turn prevented further filling of the die with granulation. This resulted in tablets having extreme weight variations. Although the spongin could not be added to the granulation prior to compression, it was very easily incorporated and granulated with the active ingredient and filler. When incorporated in this manner, the spongin did not hinder the free flowing characteristic

of the granulation, and distribution throughout the granulation was uniform. It was necessary, therefore, in those formulas containing powdered spongin, to add this agent during the process of granulation.

Since powdered synthetic sponge does not possess the same matty character as the powdered spongin, it could be added in reasonable proportions to the finished granules prior to compression. However, it was discovered that, by granulating the powdered synthetic sponge alone with a ten per cent starch paste solution using the same procedure as was used for tablet granulation, uniform sized granules were produced which could be added to the finished granulation in all proportions. Whether the powdered synthetic sponge was added in this manner or mixed with the active ingredient prior to granulation depended on the formula being prepared.

Dried corn starch when used as a disintegrant was either incorporated during granulation, after granulation, or both, again depending on the formulation in question.

Binding Agents

Four different binding agents were used in this investigation. The formulas and methods of preparing these binding agents are as follows:

I. Syrup U. S. P. - 85% (w/v)

Sucrose	85 parts
Distilled Water, a sufficient amount to make	100 parts

The syrup was prepared in accordance with the procedure given for the hot process on page 601 of the U. S. P. XIV (50).

II. Starch Paste - 10% (w/w)

Corn Starch	10 parts
Distilled Water, a sufficient amount to make	100 parts

The starch was placed in a suitable container and a sufficient quantity of cold water was slowly added. This mixture was heated slowly, with continued stirring to avoid the formation of lumps, until the solution just boiled and a translucent paste resulted. This paste was removed from the heat and allowed to cool to about 50° C., at which temperature it was used. This binding agent was freshly prepared just previous to its need.

III. Zein Solution - 5% (w/v)

Zein (corn protein)	5 parts
Isopropyl Alcohol 95%, a sufficient amount to make	100 parts

The Zein was dissolved in the isopropyl alcohol with agitation.

IV. PVP Solution - 15% (w/v)

Polyvinylpyrrolidone	15 parts
Distilled Water, a sufficient amount to make	100 parts

The PVP was added to a small amount of water and agitated until the powder was completely wetted. The remainder of water was slowly added and the mixture stirred with an electric stirrer until solution was complete.

Lubricating Agents

Two per cent magnesium stearate was selected as the lubricant in all formulations with the exception of those formulas in which the effect of lubricants on the disintegration time was being determined. For studying this property, the lubricants used in addition to magnesium stearate were talc and boric acid.

Tablet Formulation

A typical formula for compressed tablets consists of the following:

Medicinal Agent
Diluent, q. s.
Binding Agent, q. s.
Disintegrating Agent, q. s.
Lubricating Agent, q. s.

In order that a sufficient amount of information could be collected and evaluated for this investigation, it was necessary to prepare and study several different formulas. The formulas studied are found in Tables 4, 5 and 6. The letters and symbols used to describe the tablet formulas are as follows:

The letter P is used to indicate tablet formulas prepared for preliminary investigation.

The following capital letters indicate the active ingredients used in the formulas.

L	Lactose
BS	Bismuth Subcarbonate
S	Sulfadiazine
MH	Magnesium Hydroxide
CG	Calcium Gluconate
AH	Dried Aluminum Hydroxide Gel
BSN	Bismuth Subnitrate
SB	Sodium Bicarbonate

The disintegrants are represented by the following abbreviations:

A	Spongin that has been cleansed and ground.

AT Spongin that has been cleansed, bleached and ground.

AS Powdered synthetic sponge.

B Dried corn starch.

Arabic numbers indicate the percentage of disintegrant used in the formula.

Small letters are used in those formulas where a different binding agent was used for the same active ingredient.

a Syrup

b Zein Solution

c Starch Paste

d PVP Solution

The symbol / is used for those formulas in which the disintegrant was added to the finished granulation prior to compression. The capital letters and arabic numbers following this symbol indicate which agent was used and how much was added. If the disintegrant was also added to the active ingredient, it is indicated by the abbreviations preceding this symbol.

The symbol /gAS represents those formulas having granulated synthetic sponge added to the finished granulation prior to compression.

Preparing the Tablet Granulation

All tablets were made from granulations prepared by the wet process. The general procedure used for preparing a granulation was as follows:

Mixing the Dry Ingredients. -- The powdered ingredients which entered into the formula were first carefully weighed out and then put through a No. 40 mesh screen to eliminate any foreign materials and

TABLE 4

TABLE FORMULAS FOR PRELIMINARY STUDY

Formula	Per Cent Active Ingredient	Per Cent Binder	Per Cent Disintegrant	Tablet[a,b] Weight in Gm.
P-L	88.0 Lactose	10.0 Zein	---	0.341
P-L-A-7	78.8 Lactose	12.2 Zein	7.0 Spongin	0.379
P-L-A-14	70.5 Lactose	13.5 Zein	14.0 Spongin	0.423
P-BS	88.0 Bismuth Subcarbonate	10.0 Zein	---	0.341
P-BS-A-7	80.0 Bismuth Subcarbonate	11.0 Zein	7.0 Spongin	0.375
P-BS-A-14	68.9 Bismuth Subcarbonate	15.1 Zein	14.0 Spongin	0.435
P-S	88.0 Sulfadiazine	10.0 Zein	---	0.341
P-S-A-7	79.0 Sulfadiazine	12.0 Zein	7.0 Spongin	0.379
P-S-A-14	70.5 Sulfadiazine	13.5 Zein	14.0 Spongin	0.425
P-MH	70.0 Magnesium Hydroxide	28.0 Zein	---	0.428
P-MH-A-7	68.2 Magnesium Hydroxide	22.2 Zein	7.0 Spongin	0.440
P-MH-A-14	56.9 Magnesium Hydroxide	27.1 Zein	14.0 Spongin	0.500
P-CG	88.0 Calcium Gluconate	10.0 Zein	---	0.341
P-CG-A-7	81.0 Calcium Gluconate	10.0 Zein	7.0 Spongin	0.371
P-CG-A-14	71.8 Calcium Gluconate	12.2 Zein	14.0 Spongin	0.418

[a]All percentages are based on the dry weight of the finished tablet.
[b]Two per cent lubricant, based on the weight of the finished granulation, was used in all formulas.

TABLE 5

TABLET FORMULAS

Formula	Per Cent Active Ingredient	Per Cent Binder	Per Cent Disintegrant	Tablet[a,b,c] Weight in Gm.
CG-A-1	30.0 Calcium Gluconate	12.0 Syrup	1.0 Spongin	0.500
CG-A-2	30.0 Calcium Gluconate	12.2 Syrup	2.0 Spongin	0.500
CG-A-3	30.0 Calcium Gluconate	12.9 Syrup	3.0 Spongin	0.500
CG-A-4	30.0 Calcium Gluconate	13.4 Syrup	4.0 Spongin	0.500
CG-A-5	30.0 Calcium Gluconate	13.6 Syrup	5.0 Spongin	0.500
CG-A-6	30.0 Calcium Gluconate	14.7 Syrup	6.0 Spongin	0.500
CG-A-7	30.0 Calcium Gluconate	14.8 Syrup	7.0 Spongin	0.500
CG-B-15	30.0 Calcium Gluconate	13.5 Syrup	15.0 Starch	0.500
S-A-5	50.0 Sulfadiazine	19.8 Syrup	5.0 Spongin	0.600
S-A-10	50.0 Sulfadiazine	23.6 Syrup	10.0 Spongin	0.600
S-AT-5	50.0 Sulfadiazine	18.0 Syrup	5.0 Spongin	0.600
S-B-10	50.0 Sulfadiazine	21.3 Syrup	10.0 Starch	0.600
AH-A-5	43.3 Aluminum Hydroxide	24.6 Syrup	5.0 Spongin	0.693
AH-AT-5	43.3 Aluminum Hydroxide	24.3 Syrup	5.0 Spongin	0.693
AH-B-10	43.3 Aluminum Hydroxide	25.0 Syrup	10.0 Starch	0.693
AH-B-10/B-10	39.4 Aluminum Hydroxide	22.7 Syrup	18.2 Starch	0.762
BSN-AT-5-a	50.0 Bismuth Subnitrate	16.5 Syrup	5.0 Spongin	0.600
BSN-AT-5-b	50.0 Bismuth Subnitrate	27.6 Zein	5.0 Spongin	0.600
BSN-AT-5-c	50.0 Bismuth Subnitrate	21.1 Starch Paste	5.0 Spongin	0.600
BSN-AT-5-d	50.0 Bismuth Subnitrate	18.3 PVP	5.0 Spongin	0.600

(Table continued on following page)

TABLE 5 (continued)

Formula	Per Cent Active Ingredient	Per Cent Binder	Per Cent Disintegrant	Tablet[a,b,c] Weight in Gm.
BSN-AS-10-a	50.0 Bismuth Subnitrate	17.2 Syrup	10.0 Syn. Sponge	0.600
BSN-AS-10-b	50.0 Bismuth Subnitrate	29.4 Zein	10.0 Syn. Sponge	0.600
BSN-AS-10-c	50.0 Bismuth Subnitrate	23.9 Starch Paste	10.0 Syn. Sponge	0.600
BSN-AS-10-d	50.0 Bismuth Subnitrate	20.0 PVP	10.0 Syn. Sponge	0.600
BSN-B-10-a	50.0 Bismuth Subnitrate	17.4 Syrup	10.0 Starch	0.600
BSN-B-10-b	50.0 Bismuth Subnitrate	26.6 Zein	10.0 Starch	0.600
BSN-B-10-c	50.0 Bismuth Subnitrate	25.0 Starch Paste	10.0 Starch	0.600
BSN-B-10-d	50.0 Bismuth Subnitrate	20.7 PVP	10.0 Starch	0.600
SB-B-10	45.0 Sodium Bicarbonate	13.7 Syrup	10.0 Starch	0.500
SB-AT-5	45.0 Sodium Bicarbonate	12.1 Syrup	5.0 Spongin	0.500
SB-AS-5	45.0 Sodium Bicarbonate	11.6 Syrup	5.0 Syn. Sponge	0.500

[a]All percentages are based on the weight of the finished tablet.
[b]The remaining weight of the tablet was furnished by lactose.
[c]Two per cent lubricant, based on the weight of the finished granulation, was used in all formulas.

TABLE 6

TABLET FORMULAS

Formula	Per Cent Active[a] Ingredient	Per Cent[a] Binder	Per Cent[a] Disintegrant	Tablet[c] Weight in Gm.
S-A-5/gAS-5	50.0 Sulfadiazine	19.8 Syrup	5.0 Spongin 5.0 Syn. Sponge[b]	0.630
S-A-5/gAS-10	50.0 Sulfadiazine	19.8 Syrup	5.0 Spongin 10.0 Syn. Sponge[b]	0.660
BSN-AT-5-a/gAS-5	50.0 Bismuth Subnitrate	16.5 Syrup	5.0 Spongin 5.0 Syn. Sponge[b]	0.630
BSN-AT-5-a/gAS-10	50.0 Bismuth Subnitrate	16.5 Syrup	5.0 Spongin 10.0 Syn. Sponge[b]	0.660
BSN-AT-5-b/gAS-10	50.0 Bismuth Subnitrate	27.6 Zein	5.0 Spongin 10.0 Syn. Sponge[b]	0.660
BSN-AS-10-a/gAS-5	50.0 Bismuth Subnitrate	17.2 Syrup	10.0 Syn. Sponge 5.0 Syn. Sponge[b]	0.630
BSN-AS-10-a/gAS-10	50.0 Bismuth Subnitrate	17.2 Syrup	10.0 Syn. Sponge 10.0 Syn. Sponge[b]	0.660
BSN-AS-10-b/gAS-10	50.0 Bismuth Subnitrate	29.4 Zein	10.0 Syn. Sponge 10.0 Syn. Sponge[b]	0.660
BSN-B-10-a/gAS-5	50.0 Bismuth Subnitrate	17.4 Syrup	10.0 Starch 5.0 Syn. Sponge[b]	0.630
BSN-B-10-a/gAS-10	50.0 Bismuth Subnitrate	17.4 Syrup	10.0 Starch 10.0 Syn. Sponge[b]	0.660

[a]The weight per cent of ingredients is based on a 600 mg. tablet.
[b]Synthetic sponge, in a granulated state, was added to the granulation prior to compression.
[c]Tablet weight in excess of 600 mg. was contributed by the additional disintegrating agent.

reduce any lumps of powder. The powders were then combined, placed in a Stokes Granulating Mixer, and allowed to mix for one hour. The resulting mixture was next sieved through a No. 40 mesh screen to further mix and aid in proper distribution of the ingredients. The mixture of powdered ingredients was now ready for granulation.

Granulating the Dry Mixture. -- In order that the percentage of active ingredient and disintegrator remained constant for each series of formulas, it was necessary to predetermine the proportions of binding agent needed for each granulation. This was accomplished through a preliminary experiment on a small amount of each formula. With the proportion of granulating agent determined for the actual granulation process, the adjustment of diluent to obtain a specific tablet weight was calculated.

In granulating, the thoroughly mixed powdered ingredients were put in a Readco Dough Type Mixer and the granulating solution was slowly added with constant mixing. Sufficient time was allowed for the granulating solution to work in well before the next addition was made. When the mass had attained a "ball" consistency and seemed to have the proper "feel", it was considered ready for screening.

Screening the Wet Mass. -- The moistened mass was removed from the mixer, placed on a No. 8 mesh screen, and by hand, using a hard rubber spatula, forced through the screen.

Drying the Granulation. -- The coarse granules obtained from screening the wet mass were spread in thin layers on trays upon which had been laid heavy brown wrapping paper. The trays were placed in a circulatory hot air oven set at a drying temperature of 140° F. The time

required for drying varied with the nature of the granulation being dried, however, as a rule the time ranged between eight and twelve hours. During the drying period the granulation was periodically turned to assure uniform drying.

Screening the Dry Granulation. -- Following the drying period, the granulation was again hand screened, this time through a No. 14 mesh sieve. For those granulations that had a tendency to produce excessive "fines" when completely dried, it was necessary to screen the coarse granulation when it was about 3/4 or 2/3 dry. After screening a partially dried granulation it was placed back into the oven and allowed to completely dry with a minimum of fines. The granules obtained from this second screening were gently mixed by tumbling in a large jar.

Sizing the Finished Granules. -- The granulation resulting from the final screening was sized using a series of sieves. The sieves used were Nos. 20, 40, 60, 80, and 100 mesh. The sizing was accomplished by determining the percentage of the total granulation that passed through one size screen but not through the next smallest screen. For example, those granules that would not pass through a No. 40 mesh screen were recorded as 20/40 mesh granules since they passed through a No. 20 and were retained on a No. 40 mesh screen. This sizing procedure was performed on all formulas. It was noted that the size range for optimal tableting varied depending on the formulation involved. Information pertaining to the sized granulations is found in Table 7. Following the sizing of the granulation, the granules were put in a large, wide-mouth, screw-capped, brown bottle, and stored until needed at a temperature of 40° C.

Lubricating the Granulation. -- Lubrication of the granulation

TABLE 7

DESCRIPTION OF SIZED GRANULATIONS

Formula	Granulation Weight, in Grams, Previous to Sizing	Percentage of Granules within Mesh Range of				
		14/20	20/40	40/60	60/80	80/100
P-L	408	70.2	13.5	4.1	2.0	1.8
P-L-A-7	413	73.1	12.8	5.0	4.6	3.9
P-L-A-14	423	60.4	23.8	8.8	1.2	1.0
P-BS	307	65.3	20.8	6.7	2.9	1.3
P-BS-A-7	317	62.8	24.2	7.7	3.6	1.0
P-BS-A-14	341	60.3	18.9	9.4	5.3	2.2
P-S	350	66.1	11.6	6.3	8.7	4.3
P-S-A-7	352	70.4	13.9	7.5	2.2	3.4
P-S-A-14	358	71.1	20.3	2.6	1.5	3.7
P-MH	358	50.0	13.3	14.9	12.2	8.6
P-MH-A-7	361	43.0	17.7	18.4	10.5	3.0
P-MH-A-14	305	32.6	19.4	20.3	4.3	1.5
P-CG	411	50.7	31.1	9.9	4.8	3.3
P-CG-A-7	418	51.7	27.3	6.1	8.6	4.4
P-CG-A-14	392	57.4	28.1	5.0	4.0	2.7
CG-A-1	423	59.3	31.8	3.4	2.1	0.3
CG-A-2	451	58.6	22.0	9.9	4.6	2.5
CG-A-3	472	53.0	25.9	11.7	5.4	2.0
CG-A-4	323	62.5	15.7	8.3	4.2	3.1
CG-A-5	366	62.9	24.6	5.2	3.7	2.2
CG-A-6	259	68.4	20.2	6.8	2.9	0.7
CG-A-7	305	51.5	29.0	9.6	8.3	0.4
CG-B-15	285	53.3	28.3	10.1	4.7	2.6
S-A-5	439	60.1	18.5	8.5	5.5	3.4
S-A-10	452	58.4	18.9	13.2	7.4	2.0
S-AT-5	428	70.5	12.1	5.4	1.3	5.1
S-B-10	377	62.9	16.2	10.3	6.5	2.8
AH-A-5	476	60.2	18.8	10.8	4.6	2.7
AH-AT-5	429	56.0	20.1	12.1	7.2	4.4
AH-B-10	372	63.4	22.4	7.5	3.8	1.2
AH-B-10/B-10	411	51.8	31.5	4.9	7.3	2.6
BSN-AT-5-a	465	73.7	8.4	4.3	6.7	4.1
BSN-AT-5-b	372	51.5	13.7	12.1	11.4	9.3
BSN-AT-5-c	432	60.6	20.3	9.6	5.6	2.4
BSN-AT-5-d	487	75.2	11.6	8.0	1.8	1.7
BSN-AS-10-a	461	70.4	11.9	9.4	3.8	3.9
BSN-AS-10-b	388	56.0	7.5	14.7	12.3	9.2
BSN-AS-10-c	400	66.9	12.8	8.6	5.5	5.6
BSN-AS-10-d	417	73.4	9.2	9.7	3.2	1.8
BSN-B-10-a	364	68.3	17.8	6.3	1.9	5.1
BSN-B-10-b	355	60.5	22.4	8.7	2.7	1.3
BSN-B-10-c	397	62.7	20.7	5.7	5.1	4.4
BSN-B-10-d	289	71.6	13.9	2.8	7.5	3.7

was carried out immediately prior to compression. For adding the lubricant, the granulation was spread on a large sheet of heavy brown paper, the lubricant was dusted on the granules by sifting it through an 80 mesh sieve, and the entire formula was mixed well by grasping each end of the paper and gently tumbling the mixture until the granules were thoroughly covered with the lubricant. The use of an 80 mesh sieve for dusting the lubricant on the granulation not only insured the removal of any lumps that may have been present but also increased the covering power of the lubricant. Subsequent to lubrication the granulation was ready for tableting.

Compression of the Granulation

Equipment and Procedure

Description of Tablet Machines Used. -- A single punch, Eureka Hand Model, tablet machine and a rotary, Model B-2, tablet machine were used to compress the completed granulations into tablets. Both these machines are manufactured by F. J. Stokes Machine Company.

The Eureka hand operated machine had a production rate of up to 70 tablets per minute using standard concave 3/8" or 13/32" punches and dies. This machine has a maximum depth of fill of 7/16" and it can attain pressures up to one ton.

This hand operated machine was used mostly to determine the characteristics of the finished granulation before compressing it on the rotary machine. It was also useful in preparing individual tablets by hand filling the die for experimental work on formulas. This eliminated the need of filling and emptying the hopper each time a change was made

in the granulation.

The rotary, Model B-2, tablet machine produces from 350 to 500 tablets per minute and has a depth of fill up to 11/16". All tablets produced using this machine were prepared with standard concave 3/8" punches and dies. Although this machine ordinarily requires 16 sets of punches and dies, the machine can and was run with eight pairs of punches. Corks were driven into the other eight dies to prevent the granulation from falling through them. This rotary tablet machine is capable of attaining pressures of more than two tons.

Operating Adjustments Required for the Eureka Machine. -- Weight and pressure adjustments, which varied according to the particular granulation being compressed, were made by raising or lowering the punches. The speed of the machine was governed by the rate at which the hand wheel was turned and thus could be controlled as desired.

Operating Adjustments Required for the Model B-2 Machine. -- Prior to the initial use of the rotary machine, it was disassembled, cleaned, and thoroughly lubricated. From then on it was cleaned following each tablet run and lubricated according to its need.

The feed frame was set about 1/64" away from the moving die plate, while the take-off plate at the front of the feed frame was raised sufficiently to allow any granulation to pass back into the feed frame, and the scrapper at the back of the feed frame was pressed down against the table by means of a spring to keep the granulation inside the feed frame.

The hopper was set so that the gap between the funnel opening and the die plate was just large enough to allow sufficient material to flow from the hopper into the feed frame and partially fill its various

openings.

Adjustments for weight and pressure were made as follows. The exact amount of granulation needed to make one tablet was weighed and poured into the die cavity at the last opening of the feed frame just in front of the scrape-off plate. The weight adjuster was either raised or lowered until the material just filled the die cavity and was flush with the top of the die plate. The flywheel was then turned by hand until the filled die came between the compression rolls. At this point the lower roll carriage was raised by means of a pressure regulator until a tablet of proper hardness was formed.

Effects of Operating Speed on Tablets. -- In determining whether the operating speed of the rotary tablet machine manifests itself as a critical variable in the compression of certain granulations, studies were made using three different speeds. These speeds, regulated by adjusting the variable speed drive, were arbitrarily set as slow, medium, and fast, depending on the number of tablets compressed in a minute. The slow speed represented 100 tablets per minute, the medium speed 200 tablets per minute, and the fast speed 250 tablets per minute using eight sets of punches.

In this experiment, the various speeds of the rotary machine did not show any difference in the tablets produced. The weight and hardness of the tablets remained constant; the surfaces' smoothness was not affected, and the disintegration time was unaltered. Since the speed of the machine did not influence the properties of the tablets, the slow speed was selected for regular tablet runs.

Batch Uniformity. -- At frequent intervals during compression,

weight and hardness checks were made to ascertain tablet uniformity. If the weight or hardness showed a deviation from the original standards, the machine was stopped and further adjustments made until this deviation was alleviated.

Test Methods

Hardness Test

Hardness of tablets is considered to be a measure of resistance to capping, chipping or breakage under conditions of storage, packaging, and handling before actual use. A practical rule for judging proper tablet hardness is that the tablet should be readily broken when pressed between the thumb and forefinger but should not break when dropped on the floor.

In order to measure the comparative hardness of the tablets prepared in this investigation, the Monsanto Hardness Tester was used. This device is calibrated in terms of kilograms of compressional force. To determine its hardness, the tablet was centered on its vertical plane between the anvil and spring spindle. The zero reading was noted. Pressure was applied until the tablet broke. The difference between the zero and the final reading was the pressure in kilograms required to fracture the tablet. Reported values are averages of five determinations and are stated to the nearest 0.5 kilogram.

Disintegration Test

The disintegration tests were conducted in accordance with the U. S. P. XIV directions (50). The test apparatus used consists of a

basket-rack assembly which moves up and down at a rate of 31 complete cycles per minute through a distance of 5 cm. For the test, the basket assembly is immersed in a constant temperature water bath. The bath used in this investigation was maintained at 37° C. The electrically heated water bath was equipped with a mechanical stirrer and a Cenco DeKhotinsky Thermo-Regulator. Six compressed tablets were chosen at random and placed in the tubes of the basket-rack assembly. The basket was set in motion, and the time required for the tablets to completely pass through the No. 10 mesh screen was the disintegration time. Three determinations were made on all tablets tested and the average time was calculated and recorded in minutes and seconds.

The end-point for tablet disintegration has been revised in the U. S. P. XV (51) to read as follows: "the tablets are disintegrated if substantially no residue remains on the screen or if any residue that remains on the screen is a soft mass having no palpably firm core". It was obvious that this new end-point required judgment to determine what is "substantially no residue" and when a soft mass has "no palpably firm core." Since this judgment would most likely vary somewhat for each individual, it was decided to signify a tablet as being disintegrated when the tablet had completely passed through the screen. In the case of those tablets where the end-point was thought to be substantially different from that of the official end-point, a footnote was made indicating this.

Friability Test

An automatic shaking machine, simulating the most extreme handling practices, demonstrated comparative resistance ability of the tablets to

chipping and breaking.

The shaking machine completed 200 forward and backward movements per minute as it shook the tablet vials through a distance of four inches.

For the test, ten tablets were placed in a five dram vial and stoppered securely. The vial was put into the shaking compartment and the machine was operated for two 15-minute periods. After each shaking period, the tablets were sifted and blown with compressed air to remove the pulverized material. Following this treatment the tablets were weighed. The difference in weight expressed as a per cent of the original weight was designated as the friability value.

Another short series of tests were also made to determine the influence of well filled vials protected with cotton on the friability value. In this test the vial was filled to the neck with tablets and protected with a cotton filling.

Storage Test

Pharmaceutical products must be stable over extended periods of time and under varying storage conditions. To gain insight into the stability of the tablets prepared, storage studies were conducted.

The tablets tested were subjected to the following storage conditions:

a. Room temperature

b. Increased temperature

c. Decreased temperature

d. Various relative humidities

For storage tests, ten tablets were placed in an open five dram

vial and ten tablets from the same series were placed in a capped five dram vial. By storing the tablets in this manner the effect of the container on storage could be determined.

All samples stored at room temperature were placed on laboratory shelves for a specific time interval. The average room temperature during the storage period was 26.9° C. and the average relative humidity was 61.2 per cent.

In order to calculate the average room temperature and relative humidity, daily determinations of each were made for a two week period followed by semiweekly determinations for the duration of the storage studies. All relative humidity determinations were made with a sling psychrometer.

Those samples stored at elevated temperature were placed in vials and put in an electric oven at 45° C. while those stored at decreased temperature were placed in a refrigerator at 4° C. ± 1° C.

Individual desiccators were set up containing aqueous glycerin solutions (80) in varying proportions to provide relative humidities of 30, 40, 50, 80, and 95 per cent in one series of tests and 30, 45, 60, 70, 80, and 95 per cent in another series of tests. The samples, in vials, were placed in these desiccators, the desiccator covers were securely replaced, and the desiccators were placed on a shelf at room temperature.

Time intervals that the samples were stored depended on the determinations being made and are reported in the storage tables.

After specific storage intervals, the following determinations were

conducted:

a. Moisture gain or loss

b. Disintegration time

c. Hardness

To determine moisture gain or loss, each of the samples was weighed prior to storage and at subsequent intervals. The increase or decrease in weight denotes moisture gain or loss. Moisture loss is represented in the tables by a negative sign preceding the per cent weight change in tablets.

Absorption Study

The mechanism through which powdered spongin and corn starch accomplish their disintegrating action is basically the same. Both agents swell if in contact with water and as a result, when incorporated into tablets, are capable of rupturing the tablet. In order for this swelling to take place the materials must be able to absorb the water, and for this reason tests were conducted to determine the rate at which this absorption took place for each of the substances. To control the moisture conditions for the tests, several constant humidity chambers were prepared in the same manner as described earlier.

The tests were carried out by first drying the materials to constant weight at 110° C. and then placing them in each humidity chamber for 24 hours. The weight gain was calculated by reweighing the sample following this 24 hour period and was recorded as per cent of sample weight.

EXPERIMENTAL RESULTS

TABLE 8

MOISTURE ABSORBED BY POWDERED SPONGIN AND CORN STARCH AT VARIOUS RELATIVE HUMIDITIES

Relative Humidities at 27° C.	Water Absorbed After 24 hours	
	Powdered Spongin	Corn Starch
%	%	%
30	9.22	8.13
45	12.21	10.33
60	15.43	12.69
70	17.65	14.14
80	21.36	16.12
95	29.51	20.61

The results listed in Table 8 and illustrated in Figure 3 show that the moisture absorbed by powdered spongin and corn starch increased with increased relative humidities. The increase in moisture content is indicated by an S-shaped curve which is more pronounced for powdered spongin. The moisture content of the corn starch and powdered spongin before drying to constant weight was calculated as 9.76 per cent and 11.2 per cent, respectively.

Figure 3. - Absorption of Moisture by Powdered Spongin and Corn Starch

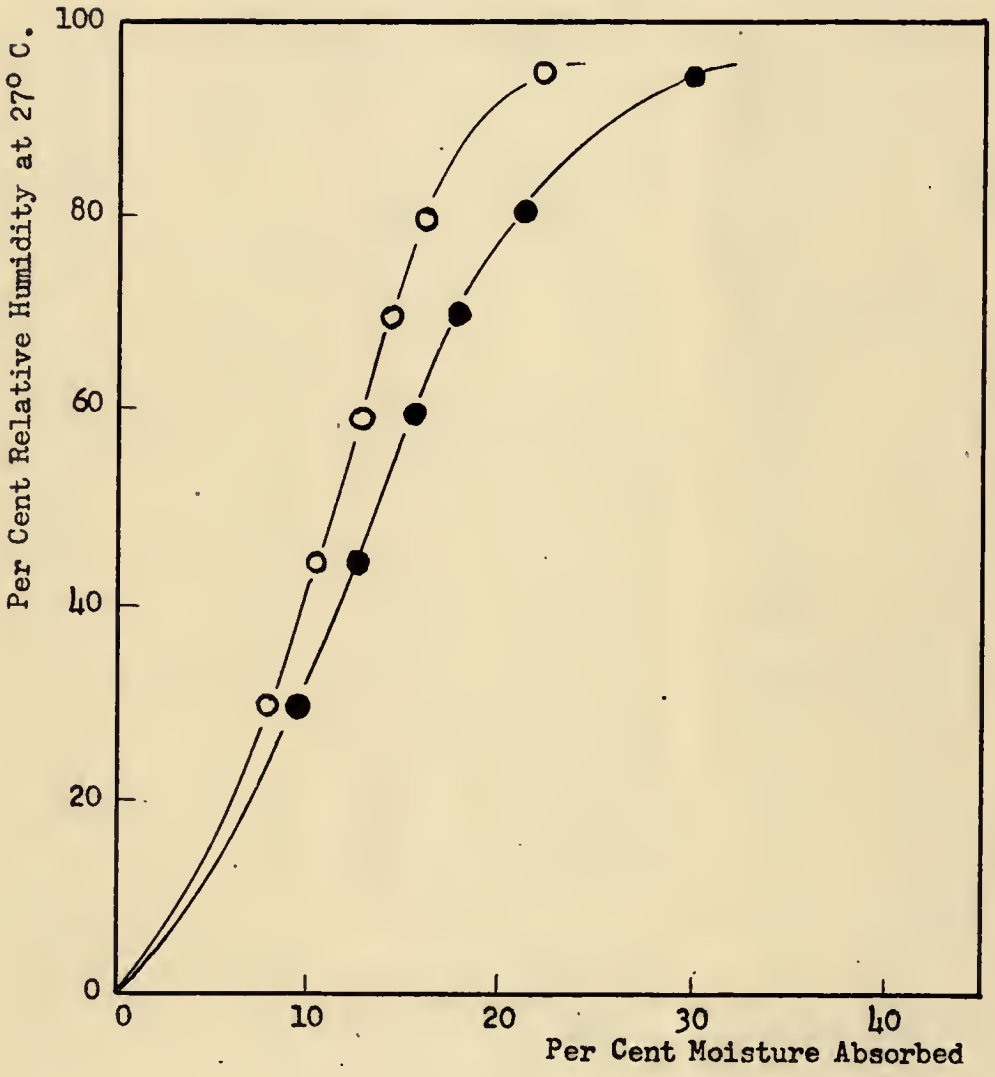


TABLE 9

A COMPARISON OF THE DISINTEGRATION TIMES OF TABLETS IMMEDIATELY AFTER COMPRESSION

Formula	Hardness	Disintegration Time
	Kg.	min.:sec.
P-L	7.0	24:23
P-L-A-7	7.0	2:35
P-L-A-14	5.0	0:48
P-BS	6.5	180:00[a]
P-BS-A-7	7.5	19:44
P-BS-A-14	7.0	8:02
P-S	7.0	180:00[a]
P-S-A-7	7.5	47:17
P-S-A-14	7.0	21:21
P-MH	6.0	180:00[a]
P-MH-A-7	6.0	2:11
P-MH-A-14	5.0	0:58
P-CG	7.0	180:00[a]
P-CG-A-7	6.0	19:23
P-CG-A-14	6.5	10:02
CG-A-1	7.0	29:20
CG-A-2	6.0	22:58
CG-A-3	6.5	17:33
CG-A-4	7.0	16:59
CG-A-5	6.5	15.26
CG-A-6	8.0	18:05
CG-A-7	7.5	13:31
CG-B-15	7.0	47:22
S-A-5	7.0	58:45
S-A-10	6.0	49:37
S-AT-5	8.0	116:21
S-B-10	7.5	98:38

(Table continued on following page)

TABLE 9 (continued)

Formula	Hardness	Disintegration Time
	Kg.	min.:sec.
AH-A-5	6.0	35:37
AH-AT-5	7.0	8:53
AH-B-10	7.0	68:04
AH-B-10/B-10	5.5	15:02
BSN-AT-5-a	6.5	35:41
BSN-AT-5-b	6.5	180:00[a]
BSN-AT-5-c	7.5	14:21
BSN-AT-5-d	7.0	12:39
BSN-AS-10-a	6.5	52:11
BSN-AS-10-b	6.0	33:05
BSN-AS-10-c	7.0	31:47
BSN-AS-10-d	6.5	20:22
BSN-B-10-a	6.0	73:51
BSN-B-10-b	6.5	180:00[a]
BSN-B-10-c	5.5	75:35
BSN-B-10-d	6.5	72:09
SB-B-10	8.5	11:11
SB-AT-5	8.0	9:07
SB-AS-5	7.5	10:35
S-A-5/gAS-5	7.0	21:44
S-A-5/gAS-10	7.0	9:08
BSN-AT-5-a/gAS-5	6.5	10:58
BSN-AT-5-a/gAS-10	7.5	6:27
BSN-AT-5-b/gAS-10	6.0	9:33
BSN-AS-10-a/gAS-5	8.0	9:56
BSN-AS-10-a/gAS-10	7.0	7:55
BSN-AS-10-b/gAS-10	6.5	10:03
BSN-B-10-a/gAS-5	7.5	8:49
BSN-B-10-a/gAS-10	6.5	6:04

[a]The disintegration test was discontinued if the tablets did not disintegrate within three hours.

TABLE 10

RELATIONSHIP BETWEEN TABLET HARDNESS, FRIABILITY AND DISINTEGRATION TIME

Formula	Hardness	Friability Value	Disintegration Time
	Kg.		min.:sec.
AH-AT-5	1.5	71.989	6:10
	2.5	9.808	4:33
	4.0	2.929	3:01
	5.5	0.913	4:49
	7.0	0.255	8:53
	9.0	0.096	14:34
	10.0	0.080	18:27
	11.0	0.077	18:58
AH-B-10	0.5	78.967	29:40
	1.5	25.861	36:00
	2.0	10.817	41:51
	2.5	1.829	49:55
	4.0	0.834	53:55
	5.5	0.626	63:27
	7.0	0.492	68:35
	9.0	0.325	75:14
BSN-AT-5-a	0.5	99.210	4:05
	1.0	96.189	3:32
	1.5	91.344	10:27
	2.5	87.273	12:08
	4.0	9.648	22:08
	5.0	1.980	27:21
	6.5	0.502	35:41
	8.0	0.260	41:14
	10.0	0.130	60:38
	12.0	0.078	62:03
BSN-B-10-a	0.5	85.935	109:00
	1.0	57.275	96:46
	2.0	16:942	65:02
	3.5	1.765	56:21
	4.5	0.998	66:14
	6.0	0.288	73:51
	8.0	0.150	88:09
	12.0	0.135	95:39

(Table continued on following page)

TABLE 10 (continued)

Formula	Hardness	Friability Value	Disintegration Time
	Kg.		min.:sec.
BSN-AT-5-b	0.5	100.000	180:00[a]
	1.5	63.541	180:00[a]
	3.0	2.381	180:00[a]
	5.0	0.349	180:00[a]
	6.5	0.205	180:00[a]
	7.5	0.131	180:00[a]
	10.0	0.127	180:00[a]
	11.0	0.104	180:00[a]
BSN-B-10-b	0.5	100.000	180:00[a]
	1.5	75.249	180:00[a]
	2.5	1.223	180:00[a]
	5.0	0.192	180:00[a]
	6.5	0.130	180:00[a]
	7.5	0.095	180:00[a]
	10.0	0.043	180:00[a]
BSN-AT-5-c	0.5	100.000	9:35
	1.0	92:137	8:52
	2.5	80.016	9:27
	3.5	3.763	6:01
	5.0	1.254	9:48
	6.5	0.997	12:53
	7.5	0.275	14:21
	9.0	0.196	18:16
	10.5	0.188	22:49
BSN-B-10-c	1.0	93.476	72:00
	1.5	86.006	74:12
	2.5	69.072	79:47
	3.5	3.555	83:24
	5.5	0.964	90:35
	6.5	0.231	98:37
	8.0	0.194	103:22
	10.5	0.088	119:17

(Table continued on following page)

TABLE 10 (continued)

Formula	Hardness	Friability Value	Disintegration Time
	Kg.		min.:sec.
BSN-AT-5-d	0.5	100.000	10:47
	1.5	91.583	9:01
	3.0	68.502	8:58
	4.5	5.229	7:36
	7.0	1.257	11:14
	8.0	0.467	15:45
	10.0	0.179	22:30
BSN-B-10-d	1.0	96.068	66:09
	3.0	80.003	73:17
	4.5	37.852	77:10
	6.5	2.207	72:09
	7.5	1.111	87:25
	8.5	0.480	94:38
	10.0	0.221	97:07
	11.0	0.099	107:03

[a]The disintegration test was discontinued if the tablets did not disintegrate within three hours.

Figure 4. - Relationship Between Disintegration Time and Tablet Hardness for Tablets Prepared with Spongin as the Disintegrant Showing a Minimum Point in the Curve.

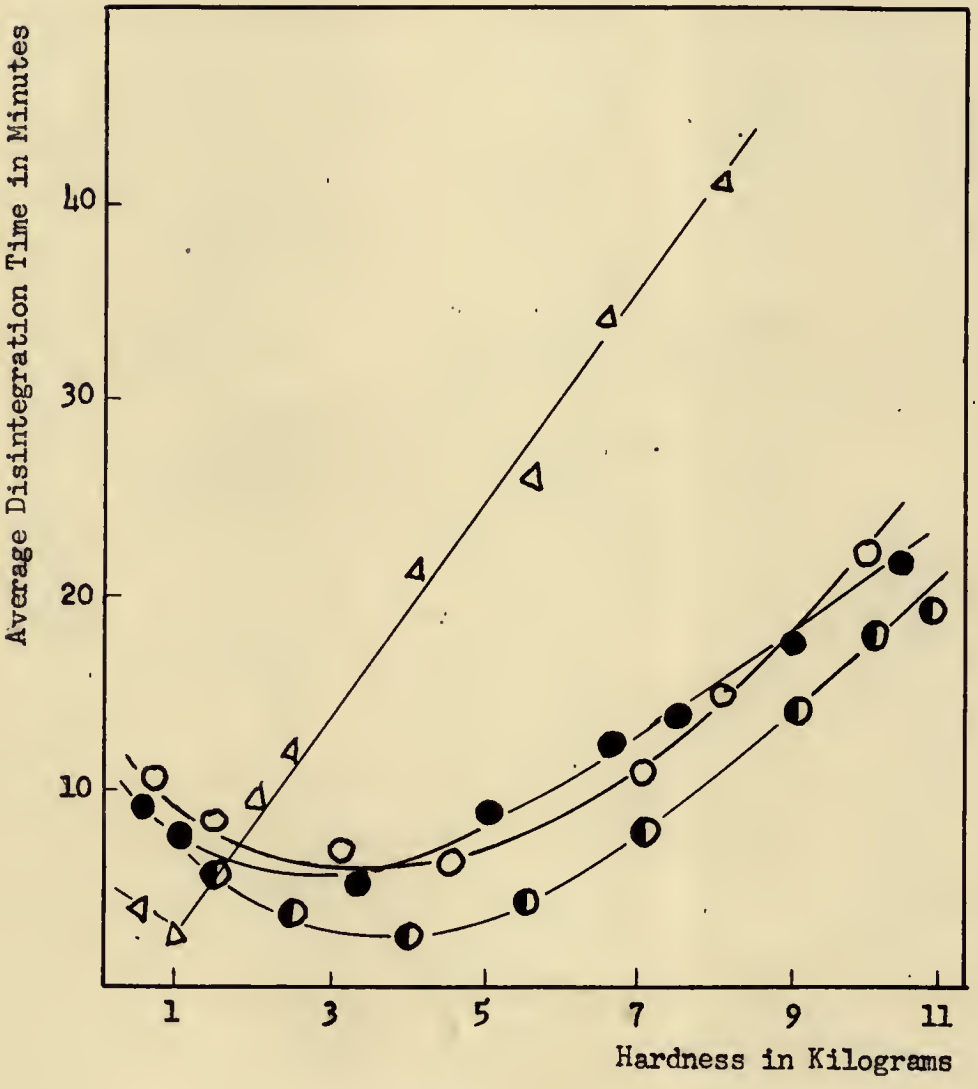


Figure 5. - Tablets Prepared with Corn Starch as the Disintegrant showing a Linear Relationship Between Disintegration Time and Tablet Hardness

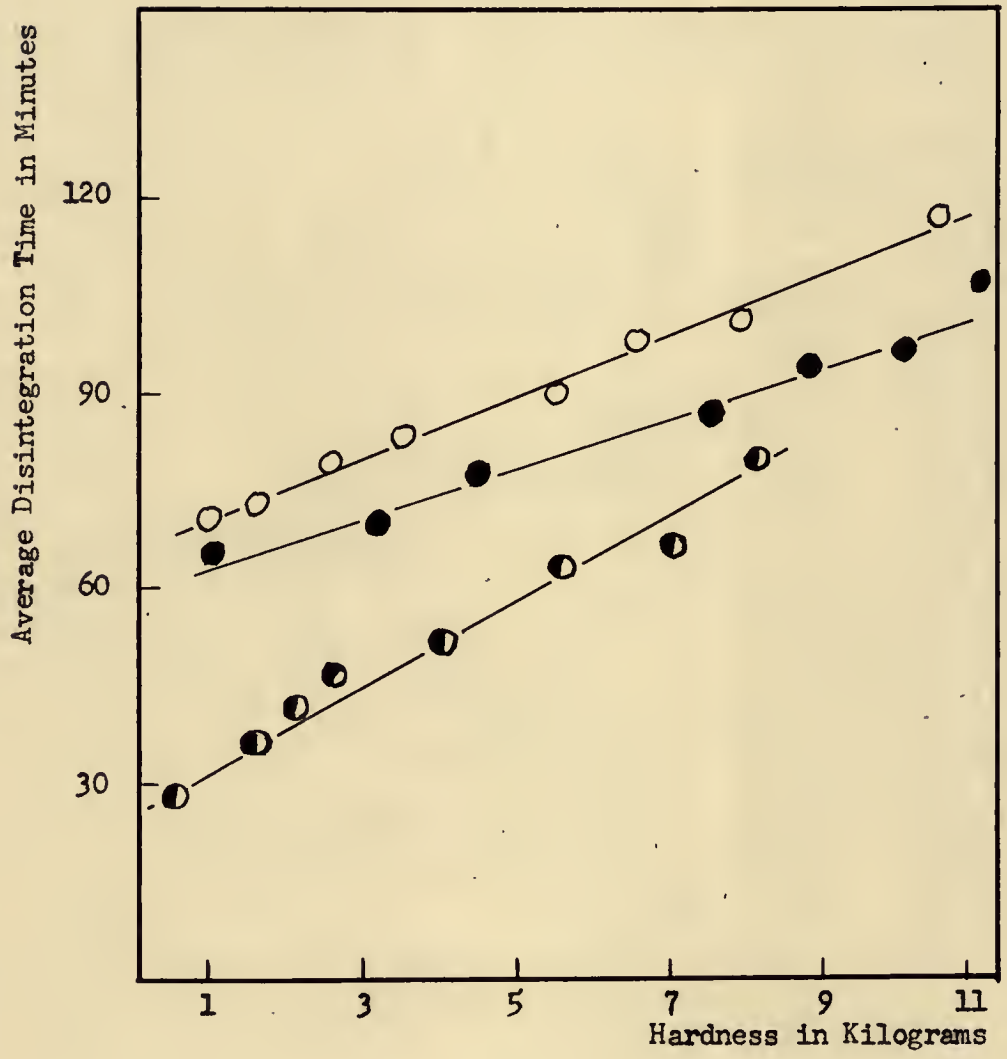
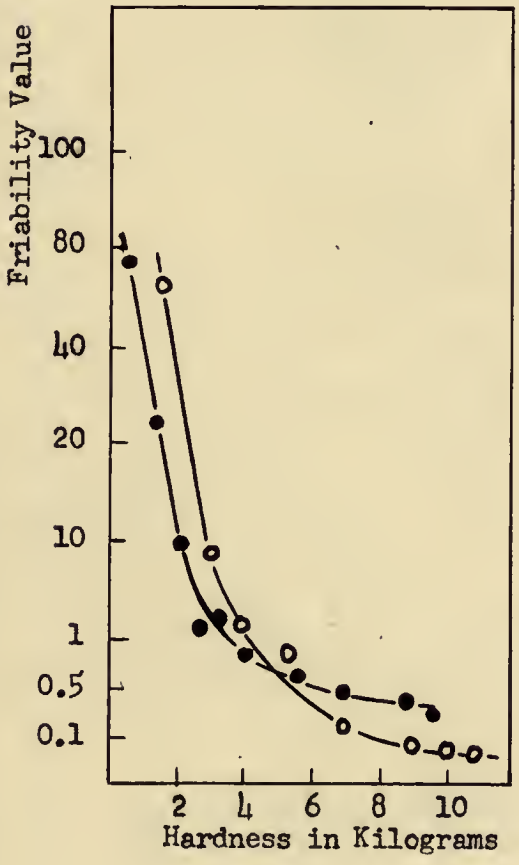


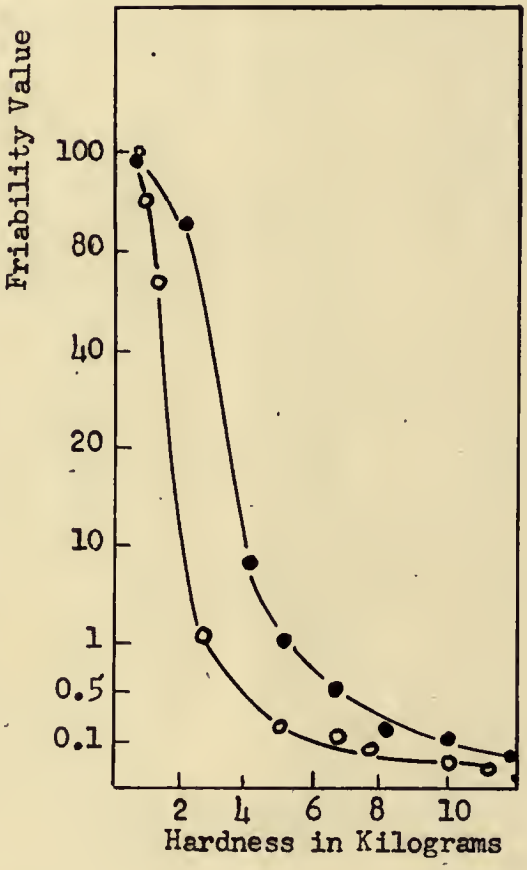
Figure 6. - Relationship Between Tablet Friability and Tablet Hardness



● AH-B-10

○ AH-AT-5

Figure 7. - Relationship Between Tablet Friability and Tablet Hardness



● BSN-AT-5-a

○ BSN-B-10-b

TABLE 11

FRIABILITY VALUES AFTER TWO SHAKING PERIODS

Formula	Hardness	Friability Value	
		After 15 Minutes	After 30 Minutes
	Kg.		
S-A-5	5.0	0.038	0.178
S-B-10	5.0	0.115	0.214
AH-AT-5	7.0	0.255	0.501
AH-B-10	7.0	0.493	0.739
BSN-AS-10-a	8.0	0.438	0.742
BSN-AS-10-b	7.5	0.183	0.354
BSN-AS-10-c	7.5	0.679	1.099
BSN-AS-10-d	7.0	0.244	0.367
BSN-AT-5-a	6.5	0.502	1.218
BSN-AT-5-b	6.5	0.205	0.351
BSN-AT-5-c	6.5	0.997	2.093
BSN-AT-5-d	7.0	0.301	0.521
BSN-B-10-a	6.0	0.288	0.492
BSN-B-10-b	6.5	0.130	0.217
BSN-B-10-c	6.5	0.231	0.488
BSN-B-10-d	6.0	0.194	0.316

TABLE 12

FRIABILITY VALUES OF TABLETS PROTECTED WITH A COTTON FILLER IN VIALS

Formula	Hardness	Friability Value After 15 Minutes
	Kg.	
S-A-5	5.0	0.002
S-B-10	5.0	0.000
AH-AT-5	7.0	0.000
AH-B-10	7.0	0.000
BSN-AS-10-a	8.0	0.000
BSN-AT-5-a	6.5	0.006
BSN-B-10-a	6.0	0.003

TABLE 13

COMPARISON OF DISINTEGRATION RATES OF TABLETS PREPARED WITH DIFFERENT BINDING AGENTS

Formula	Hardness	Binder	Disintegration Time
	Kg.		min.:sec.
BSN-AT-5-a	6.5	Syrup	35:41
BSN-AT-5-b	6.5	Zein Solution	180:00[a]
BSN-AT-5-c	6.5	Starch Paste	12:53
BSN-AT-5-d	7.0	PVP Solution	12:39
BSN-B-10-a	6.0	Syrup	73:51
BSN-B-10-b	6.5	Zein Solution	180:00[a]
BSN-B-10-c	6.5	Starch Paste	89:37
BSN-B-10-d	6.5	PVP Solution	72:09
BSN-AS-10-a	6.5	Syrup	52:11
BSN-AS-10-b	6.0	Zein Solution	33:05
BSN-AS-10-c	7.0	Starch Paste	31:47
BSN-AS-10-d	6.5	PVP Solution	20:22

[a]The disintegration test was discontinued if the tablets did not disintegrate within three hours.

TABLE 14

COMPARISON OF DISINTEGRATION RATES OF TABLETS PREPARED WITH DIFFERENT LUBRICATING AGENTS

Formula	Hardness	Lubricating Agent	Disintegration Time
	Kg.		min.:sec.
AH-AT-5	7.5	Magnesium Stearate	8:53
	7.0	Talc	6:23
	7.0	Boric Acid	2:30
	7.0	None	4:02
BSN-AT-5-a	6.5	Magnesium Stearate	32:14
	6.5	Talc	9:24
	7.0	Boric Acid	8:53
	6.0	None	6:59
BSN-AS-10-c	7.0	Magnesium Stearate	23:01
	6.5	Talc	9:44
	7.5	Boric Acid	5:57
	8.0	None	5:00
BSN-B-10-a	6.0	Magnesium Stearate	46:19
	6.5	Talc	9:46
	6.5	Boric Acid	7:45
	7.0	None	5:08
SB-B-10	8.5	Magnesium Stearate	11:11
	7.0	Talc	8:33
	6.5	Boric Acid	4:07
	6.5	None	3:25
SB-AT-5	8.0	Magnesium Stearate	9:07
	7.5	Talc	6:55
	7.0	Boric Acid	3:00
	7.5	None	3:21

Figures 8, 9 and 10. - Comparative Disintegration Rates for Differently Lubricated Tablets

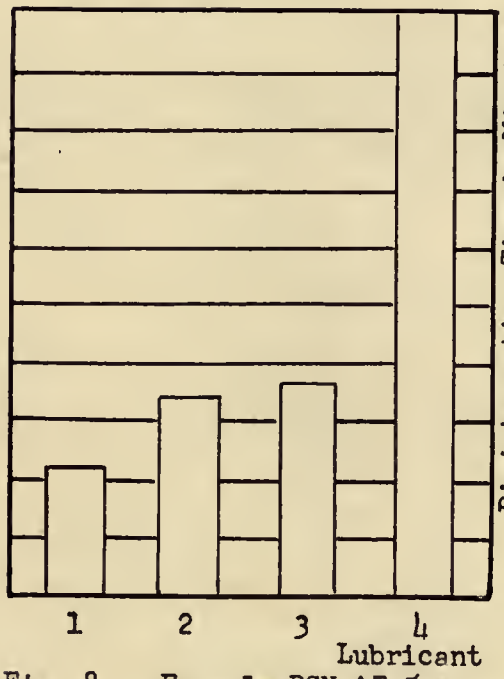


Fig. 8. - Formula BSN-AT-5-a

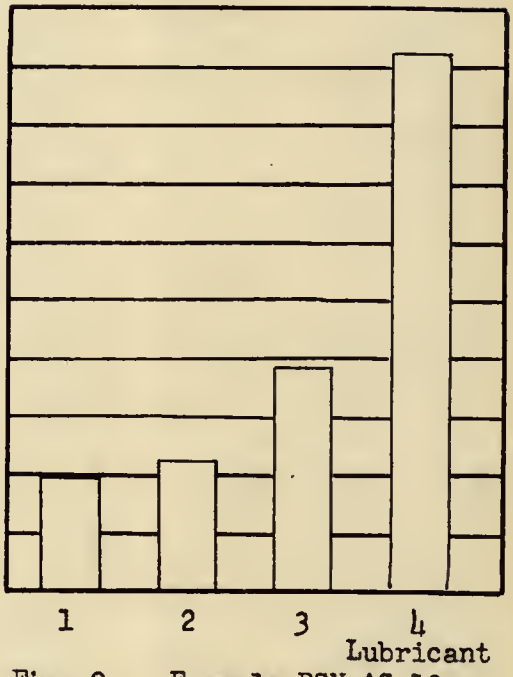


Fig. 9. - Formula BSN-AS-10-c

Fig. 10. - Formula SB-B-10

KEY TO LUBRICANTS USED

1 - No lubricant

2 - Boric Acid

3 - Talc

4 - Magnesium Stearate

TABLE 15

TABLET DISINTEGRATION TIMES AFTER STORAGE FOR INTERVALS OF 250, 500 AND 750 HOURS IN OPEN VIALS AT VARIOUS TEMPERATURE CONDITIONS

Formula	Hardness	Storage Time	Disintegration Time			
			Originally	After Storage at 27° C.	After Storage at 45° C.	After Storage at 5° C.
	Kg.	hrs.	min.:sec.	min.:sec.	min:sec.	min.:sec.
CG-A-2	10.0	250	25:23	31:56	26:37	26:09
		500	25:23	26:18	27:20	26:52
		750	25:23	30:42	27:37	27:08
CG-A-4	9.5	250	22:58	29:59	23:10	23:01
		500	22:58	24:41	24:07	22:52
		750	22:58	27:58	24:40	23:05

TABLE 16

TABLET DISINTEGRATION TIMES AFTER STORAGE FOR INTERVALS OF 250, 500 AND 750 HOURS IN CLOSED VIALS AT VARIOUS TEMPERATURE CONDITIONS

Formula	Hardness	Storage Time	Disintegration Time			
			Originally	After Storage at 27° C.	After Storage at 45° C.	After Storage at 5° C.
	Kg.	hrs.	min.:sec.	min.:sec.	min.:sec.	min.:sec.
CG-A-2	10.0	250	25:23	29:44	27:18	27:11
		500	25:23	25:12	27:42	27:00
		750	25:23	27:53	28:33	28:14
CG-A-4	9.5	250	22:58	28:46	23:18	23:01
		500	22:58	25:01	23:46	23:04
		750	22:58	26:01	24:34	23:42

TABLE 17

TABLET DISINTEGRATION TIMES AFTER STORAGE FOR INTERVALS OF 250, 500 AND 750 HOURS IN OPEN VIALS AT VARIOUS RELATIVE HUMIDITIES

Formula	Hardness	Storage Time	Original Disintegration Time	Disintigration Times After Storage Relative Humidities at 27° C.				
				30%	40%	50%	80%	95%
	Kg.	hrs.	min.:sec.	min.:sec.	min.:sec.	min.:sec.	min.:sec.	min.:sec.
CG-A-2	10.0	250	25:23	25:27	30:56	29:48	31:43	46:06
		500	25:23	25:49	31:28	31:31	32:08	57:51
		750	25:23	25:53	32:39	31:59	33:47	180:00[a]
CG-A-3	8.5	250	23:39	23:21	25:10	25:23	28:40	30:05
		500	23:39	25:52	26:08	27:31	28:21	55:44
		750	23:39	27:21	28:29	27:58	28:40	180:00[a]
CG-A-4	9.5	250	22:58	26:21	26:00	23:06	30:08	49:11
		500	22:58	26:32	28:17	28:11	34:51	58:26
		750	22:58	27:05	30:06	28:41	38:23	180:00[a]

[a]The disintegration test was discontinued if the tablets did not disintegrate within three hours.

TABLE 18

TABLET DISINTEGRATION TIMES AFTER STORAGE FOR INTERVALS OF 250, 500 AND 750 HOURS IN CLOSED VIALS AT VARIOUS RELATIVE HUMIDITIES

Formula	Hardness	Storage Time	Original Disintegration Time	Disintegration Times After Storage				
				Relative Humidities at 27° C.				
				30%	40%	50%	80%	95%
	Kg.	hrs.	min.:sec.	min.:sec.	min.:sec.	min.:sec.	min.:sec.	min.:sec.
CG-A-2	10.0	250	25:23	25:29	30:24	25:57	30:22	30:00
		500	25:23	25:52	31:15	28:00	33:01	30:01
		750	25:23	28:10	32:22	28:20	33:56	31:10
CG-A-3	8.5	250	23:39	22:51	23:16	24:59	24:31	23:13
		500	23:39	25:30	26:19	25:01	25:11	23:33
		750	23:39	29:05	27:39	26:00	26:05	24:01
CG-A-4	9.5	250	22:58	24:36	24:58	24:12	23:33	24:21
		500	22:58	25:07	25:09	24:18	25:23	27:39
		750	22:58	26:25	25:28	24:47	25:54	26:20

TABLE 19

CHANGES IN TABLET HARDNESS AFTER STORAGE FOR INTERVALS OF 250, 500 AND 750 HOURS AT VARIOUS RELATIVE HUMIDITIES

Formula	Storage Time	Original Hardness	Tablet Hardness After Storage (Kilograms) Relative Humidities at 27° C.									
			30%	40%	50%	80%	95%	30%	40%	50%	80%	95%
	hrs.	Kg.	Open Vials					Closed Vials				
CG-A-2	250	10.0	9.0	10.0	4.0	5.5	2.5	10.0	10.5	10.5	10.0	10.0
	500	10.0	9.0	8.5	3.0	4.0	1.0	10.0	11.0	12.0	10.0	10.5
	750	10.0	6.5	8.0	3.0	1.0	---[a]	11.0	12.5	12.0	10.5	10.5
CG-A-3	250	8.0	8.5	8.0	9.0	6.5	5.0	8.0	8.0	9.5	9.0	8.0
	500	8.0	8.5	8.0	9.5	4.0	2.0	9.0	9.0	11.0	9.5	8.0
	750	8.0	9.0	7.0	13.5	2.0	---[a]	10.0	10.0	11.5	10.5	8.0
CG-A-4	250	7.5	7.5	7.5	5.5	2.5	2.0	7.5	8.0	7.5	7.5	7.5
	500	7.5	7.0	6.5	4.5	1.5	---[a]	7.5	8.5	7.5	7.5	7.5
	750	7.5	6.5	4.5	2.0	1.5	---[a]	7.5	8.5	7.5	8.0	7.0

[a] Tablets had a soft soggy consistency and could not be tested.

TABLE 20

CHANGES IN TABLET WEIGHT AFTER STORAGE AT VARIOUS RELATIVE HUMIDITIES

Formula	Storage Time	Per Cent Change in Weight After Storage									
		Relative Humidities at 27° C.									
		30%	40%	50%	80%	95%	30%	40%	50%	80%	95%
	hrs.	Open Vials					Closed Vials				
S-A-5	24	0.00	0.00	0.00	0.21	3.07	0.00	0.00	0.00	0.00	0.00
	96	0.00	0.00	0.00	1.04	7.58	0.00	0.00	0.00	0.00	0.00
	250	0.00	0.00	0.00	1.09	12.66	0.00	0.00	0.00	0.00	0.00
	500	0.00	0.00	0.00	2.03	25.74	0.00	0.00	0.00	0.00	0.61
S-B-10	24	-1.73	-1.38	-0.92	-0.50	3.73	0.00	0.00	0.00	0.00	0.00
	72	-1.74	-1.71	-0.99	-0.50	4.43	0.00	0.00	0.00	0.00	0.00
	96	-1.74	-1.71	-0.98	-0.97	4.49	0.00	0.00	0.00	0.00	0.00
	250	-1.74	-1.71	-0.87	-1.28	11.06	-0.42	-0.17	-0.16	-0.13	0.00
	500	-1.74	-1.71	-1.72	-1.28	-----[a]	-0.50	-0.24	-0.24	-0.22	0.29
	1000	-1.74	-1.71	-1.72	-1.28	-----[a]	-0.50	-0.24	-0.24	-0.22	0.29
AH-A-5	24	0.08	0.59	0.78	1.66	2.18	0.00	0.00	0.00	0.00	0.00
	48	0.28	0.59	0.78	1.78	3.10	0.00	0.00	0.00	0.00	0.00
	72	0.28	0.59	0.78	1.78	5.17	0.00	0.00	0.00	0.00	0.00
	96	0.28	0.59	0.78	1.87	8.23	0.00	0.00	0.00	0.00	0.00
	250	0.28	0.59	0.78	2.07	17.86	0.00	0.00	0.00	0.00	0.00
	500	0.28	0.59	0.78	2.07	23.55	0.00	0.00	0.00	0.00	0.00
	750	0.28	0.59	0.78	2.07	-----[a]	0.00	0.00	0.00	0.00	0.00
	1000	0.28	0.59	0.78	2.07	-----[a]	0.00	0.00	0.00	0.00	0.00

[a]Tablets were soggy and moldy and adhered within the container.

TABLE 21

CHANGES IN TABLET WEIGHT, HARDNESS AND DISINTEGRATION TIME
AFTER STORAGE FOR INTERVALS OF 500 AND 1000 HOURS
IN OPEN VIALS AT VARIOUS TEMPERATURE CONDITIONS

Formula	Storage Time	Storage Temperature	Weight Change	Hardness		Disintegration Time	
				Original	Resultant	Original	Resultant
	hrs.		%	Kg.	Kg.	min.:sec.	min.:sec.
S-A-5	500	R. T.[a]	0.00	5.0	5.0	66:42	70:56
		45° C.	-0.29	5.0	7.0	66:42	54:32
		5° C.	0.00	5.0	5.0	66:42	110:43
	1000	R. T.[a]	0.00	5.0	4.5	66:42	60:08
		45° C.	-0.12[b]	5.0	7.0	66:42	62:28
		5° C.	0.00	5.0	5.0	66:42	115:11
S-B-10	500	R. T.[a]	-2.23	5.0	11.0	80:54	122:36
		45° C.	-2.49	5.0	12.5	80:54	148:29
		5° C.	-1.69	5.0	10.5	80:54	143:53
	1000	R. T.[a]	-2.23	5.0	11.0	80:54	123:05
		45° C.	-2.49	5.0	12.5	80:54	149:48
		5° C.	-1.69	5.0	10.0	80:54	128:32

[a]Room Temperature.

[b]In general the tablets were removed from the oven and allowed to cool to room temperature before weighing; however, these tablets remained at room temperature for over an hour before weighing.

TABLE 22

CHANGES IN TABLET WEIGHT, HARDNESS AND DISINTEGRATION TIME AFTER STORAGE FOR INTERVALS OF 500 AND 1000 HOURS IN CLOSED VIALS AT VARIOUS TEMPERATURE CONDITIONS

Formula	Storage Time	Storage Temperature	Weight Change	Hardness		Disintegration Time	
				Original	Resultant	Original	Resultant
	hrs.		%	Kg.	Kg.	min.:sec.	min.:sec.
S-A-5	500	R. T.[a]	0.00	5.0	5.0	66:42	59:43
		45° C.	0.00	5.0	5.0	66:42	65:22
		5° C.	0.00	5.0	5.0	66:42	40:35
	1000	R. T.[a]	0.00	5.0	5.0	66:42	58:58
		45° C.	0.00	5.0	5.0	66:42	69:33
		5° C.	0.00	5.0	5.0	66:42	70:06
S-B-10	500	R. T.[a]	-0.25	5.0	5.5	80:54	106:15
		45° C.	-0.49	5.0	5.5	80:54	149:01
		5° C.	-0.24	5.0	5.5	80:54	120:50
	1000	R. T.[a]	-0.25	5.0	5.5	80:54	121:48
		45° C.	-0.74	5.0	6.5	80:54	165:53
		5° C.	-0.24	5.0	5.5	80:54	135:58

[a]Room Temperature.

TABLE 23

CHANGES IN TABLET WEIGHT, HARDNESS AND DISINTEGRATION TIME AFTER STORAGE FOR 1000 HOURS IN OPEN VIALS AT VARIOUS RELATIVE HUMIDITIES

Formula	Relative Humidity at 27° C.	Weight Change	Hardness		Disintegration Time	
			Original	Resultant	Original	Resultant
	%	%	Kg.	Kg.	min.:sec.	min.:sec.
S-A-5	30	0.00	5.0	5.5	66:42	55:32
	40	0.00	5.0	5.0	66:42	62:18
	50	0.00	5.0	5.0	66:42	70:50
	80	2.30	5.0	2.5	66:42	80:44
	95	----[a]	5.0	---[a]	66:42	-----[a]
S-B-10	30	-1.74	5.0	10.5	80:54	188:28
	40	-1.71	5.0	9.5	80:54	140:33
	50	-1.72	5.0	10.5	80:54	180:16
	80	-1.28	5.0	5.5	80:54	135:52
	95	----[a]	5.0	---[a]	80:54	------[a]

[a]Tablets were soggy and moldy and adhered within the container.

TABLE 24

CHANGES IN TABLET WEIGHT, HARDNESS AND DISINTEGRATION TIME
AFTER STORAGE FOR 1000 HOURS IN CLOSED VIALS
AT VARIOUS RELATIVE HUMIDITIES

Formula	Relative Humidity at 27° C.	Weight Change	Hardness		Disintegration Time	
			Original	Resultant	Original	Resultant
	%	%	Kg.	Kg.	min.:sec.	min.:sec.
S-A-5	30	0.00	5.0	6.0	66:42	49:58
	40	0.00	5.0	5.5	66:42	59:01
	50	0.00	5.0	5.5	66:42	58:46
	80	0.00	5.0	6.5	66:42	63:23
	95	0.62	5.0	4.0	66:42	95:16
S-B-10	30	-0.50	5.0	5.0	80:54	105:36
	40	-0.24	5.0	4.5	80:54	140:35
	50	-0.24	5.0	4.0	80:54	142:14
	80	-0.22	5.0	4.5	80:54	120:59
	95	0.29	5.0	3.5	80:54	165:22

TABLE 25

CHANGES IN TABLET WEIGHT, HARDNESS AND DISINTEGRATION TIME AFTER STORAGE FOR INTERVALS OF 500 AND 1000 HOURS IN OPEN VIALS AT VARIOUS TEMPERATURE CONDITIONS

Formula	Storage Time	Storage Temperature	Weight Change	Hardness		Disintegration Time	
				Original	Resultant	Original	Resultant
	hrs.		%	Kg.	Kg.	min.:sec.	min.:sec.
AH-AT-5	500	R. T.[a]	-0.45	7.0	8.5	8:53	11:47
		45° C.	-0.69	7.0	9.5	8:53	10:06
		5° C.	0.84	7.0	6.5	8:53	22:15
	1000	R. T.[a]	-0.13	7.0	8.0	8:53	9:11
		45° C.	-0.76	7.0	10.0	8:53	18:29
		5° C.	0.91	7.0	6.5	8:53	25:37
AH-B-10	500	R. T.[a]	0.18	7.0	7.0	68:04	69:36
		45° C.	-0.36	7.0	6.0	68:04	72:55
		5° C.	0.18	7.0	7.0	68:04	69:43
	1000	R. T.[a]	-0.16	7.0	6.0	68:04	77:15
		45° C.	-0.54	7.0	7.0	68:04	79:02
		5° C.	0.11	7.0	5.5	68:04	69:59

[a]Room Temperature.

TABLE 26

CHANGES IN TABLET WEIGHT, HARDNESS AND DISINTEGRATION TIME AFTER STORAGE FOR INTERVALS OF 500 AND 1000 HOURS IN CLOSED VIALS AT VARIOUS TEMPERATURE CONDITIONS

Formula	Storage Time	Storage Temperature	Weight Change	Hardness		Disintegration Time	
				Original	Resultant	Original	Resultant
	hrs.		%	Kg.	Kg.	min.:sec.	min.:sec.
AH-AT-5	500	R. T.[a]	0.00	7.0	7.5	8:53	10:46
		45° C.	-0.25	7.0	8.0	8:53	10:31
		5° C.	0.00	7.0	7.5	8:53	14:08
	1000	R. T.[a]	0.00	7.0	7.0	8:53	11:53
		45° C.	-0.51	7.0	7.5	8:53	9:54
		5° C.	0.00	7.0	6.5	8:53	16:25
AH-B-10	500	R. T.[a]	0.00	7.0	7.0	68:04	69:05
		45° C.	-0.11	7.0	7.0	68:04	74:54
		5° C.	0.00	7.0	7.0	68:04	68:09
	1000	R. T.[a]	0.00	7.0	7.0	68:04	69:11
		45° C.	-0.18	7.0	7.0	68:04	76:49
		5° C.	0.00	7.0	7.0	68:04	70:56

[a]Room Temperature.

TABLE 27

CHANGES IN TABLET WEIGHT, HARDNESS AND DISINTEGRATION TIME
AFTER STORAGE FOR 1000 HOURS IN OPEN VIALS
AT VARIOUS RELATIVE HUMIDITIES

Formula	Relative Humidity at 27° C.	Weight Change	Hardness		Disintegration Time	
			Original	Resultant	Original	Resultant
	%	%	Kg.	Kg.	min.:sec.	min.:sec.
AH-AT-5	30	-0.26	7.0	6.5	8:53	15:26
	45	-0.06	7.0	7.0	8:53	12:55
	60	0.19	7.0	7.0	8:53	14:04
	80	0.78	7.0	6.0	8:53	16:08
	95	----[a]	7.0	---[a]	8:53	-----[a]

[a]Tablets were soggy and moldy and adhered within the container.

TABLE 28

CHANGES IN TABLET WEIGHT, HARDNESS AND DISINTEGRATION TIME
AFTER STORAGE IN CLOSED VIALS FOR 1000 HOURS
AT VARIOUS RELATIVE HUMIDITIES

Formula	Relative Humidity at 27° C.	Weight Change	Hardness		Disintegration Time	
			Original	Resultant	Original	Resultant
	%	%	Kg.	Kg.	min.:sec.	min.:sec.
AH-AT-5	30	-0.03	7.0	7.0	8:53	9:24
	45	0.00	7.0	7.0	8:53	12:09
	60	0.00	7.0	6.5	8:53	13:00
	80	0.00	7.0	6.5	8:53	14:33
	95	0.73	7.0	6.0	8:53	16:27

TABLE 29

CHANGES IN TABLET WEIGHT, HARDNESS AND DISINTEGRATION TIME AFTER STORAGE FOR 1000 HOURS IN OPEN VIALS AT VARIOUS RELATIVE HUMIDITIES

Formula	Relative Humidity at 27° C.	Weight Change	Hardness		Disintegration Time	
			Original	Resultant	Original	Resultant
	%	%	Kg.	Kg.	min.:sec.	min.:sec.
AH-A-5	30	0.28	13.5	12.5	42:17	41:02
	40	0.59	13.5	12.0	42:17	49:20
	50	0.78	13.5	11.0	42:17	52:33
	80	2.07	13.5	4.0	42:17	83:32
	95	----[a]	13.5	---[a]	42:17	-----[a]
AH-B-10	30	0.10	7.0	7.0	68:04	68:51
	40	0.18	7.0	7.0	68:04	69:02
	50	0.19	7.0	7.0	68:04	70:00
	80	0.74	7.0	4.0	68:04	101:35
	95	----[a]	7.0	---[a]	68:04	-----[a]

[a]Tablets were soggy and moldy and adhered within the container.

TABLE 30

CHANGES IN TABLET WEIGHT, HARDNESS AND DISINTEGRATION TIME
AFTER STORAGE FOR 1000 HOURS IN CLOSED VIALS
AT VARIOUS RELATIVE HUMIDITIES

Formula	Relative Humidity at 27° C.	Weight Change	Hardness		Disintegration Time	
			Original	Resultant	Original	Resultant
	%	%	Kg.	Kg.	min.:sec.	min.:sec.
AH-A-5	30	0.00	13.5	12.5	42:17	41:56
	40	0.00	13.5	13.0	42:17	41:39
	50	0.00	13.5	13.0	42:17	41:22
	80	0.00	13.5	13.0	42:17	41:40
	95	0.36	13.5	10.0	42:17	44:08
AH-B-10	30	0.00	7.0	7.0	68:04	70:11
	40	0.00	7.0	7.0	68:04	68:01
	50	0.00	7.0	7.5	68:04	68:47
	80	0.00	7.0	7.0	68:04	69:01
	95	0.19	7.0	6.0	68:04	70:02

TABLE 31

CHANGES IN TABLET WEIGHT OF DIFFERENTLY LUBRICATED TABLETS AFTER STORAGE FOR 500 HOURS IN OPEN VIALS AT VARIOUS TEMPERATURE CONDITIONS

Formula	Storage Temperature	Weight Change in Tablets[a]		
		Unlubricated	Lubricated with Magnesium Stearate	Lubricated with Boric Acid
		%	%	%
BSN-AT-5-a	R. T.[b]	0.21	0.71	1.40
	45° C.	-0.22	0.00	-0.26
	5° C.	0.59	0.69	0.69
BSN-AS-10-a	R. T.[b]	0.46	0.78	0.12
	45° C.	-0.48	-0.59	-1.28
	5° C.	0.34	0.58	0.37
BSN-B-10-a	R. T.[b]	0.11	0.30	0.10
	45° C.	-0.39	-0.19	-0.39
	5° C.	0.39	0.29	0.31

[a]The tablets tested were within a hardness range of 6.0 and 7.5 Kg.

[b]Room Temperature.

TABLE 32

CHANGES IN TABLET WEIGHT OF DIFFERENTLY LUBRICATED TABLETS
AFTER STORAGE FOR 500 HOURS IN OPEN VIALS
AT VARIOUS RELATIVE HUMIDITIES

Formula	Relative Humidity at 27° C.	Weight Change in Tablets[a]		
			Lubricated with	
		Unlubricated	Magnesium Stearate	Boric Acid
	%	%	%	%
BSN-AT-5-a	30	0.22	0.28	0.13
	45	0.58	0.42	0.41
	60	0.77	0.56	0.55
	70	0.93	0.98	0.67
	80	1.62	1.85	2.11
	95	----[b]	13.22	----[b]
BSN-AS-10-a	30	0.00	0.00	0.24
	45	0.34	0.38	0.00
	60	0.91	0.96	0.73
	70	1.38	1.52	1.29
	80	2.23	2.69	2.37
	95	----[b]	9.34	----[b]
BSN-B-10-a	30	0.00	0.00	0.00
	45	0.16	0.20	0.00
	60	0.41	0.40	0.30
	70	0.69	0.49	0.39
	80	1.11	1.22	1.09
	95	----[b]	9.55	----[b]

[a] The tablets tested were within a hardness range of 6.0 and 7.5 Kg.

[b] Tablets were soggy and adhered within the container.

DISCUSSION OF RESULTS

Bleaching of Sponge

Although an acidified solution of sodium bisulfite was found to satisfactorily bleach the cleansed sponge without any further treatment, it was noted that on standing for three to five days the bleached sponge acquired a yellowish color.

The following reaction took place when a sodium bisulfite solution was treated with hydrochloric acid:

$$NaHSO_3 + HCl \longrightarrow NaCl + SO_2 + H_2O$$

It was the sulfurous acid formed that served as the bleaching agent. Since exposure of the sponge to air, after being bleached with this agent, resulted in the gradual return of the yellowish color, it was assumed that the pigment was not destroyed, but instead, reduced or converted into a colorless compound. It is probably through a reoxidation process that this colorless compound is restored to its original pigment state. If such is the case, this would account for the return of the yellowish color when the bleached sponge was exposed to air.

When a potassium permanganate solution was used for bleaching, the sponge remained in an almost white condition indefinately. Potassium permanganate, contrary to sulfurous acid, produces its bleaching effect through an oxidation process. The action of potassium permanganate is through the liberation of nascent oxygen which takes place as follows:

$$2KMnO_4 + 3H_2O \longrightarrow 2KOH + 2MnO_2.H_2O + 3O$$

The brown deposit that remained on the sponge following the permanganate treatment was due to the precipitation of hydrated manganese dioxide. In order to remove this brown deposit it was necessary to subsequently place the sponge in a sodium bisulfite bath. This reduced the manganese compound to a colorless soluble salt which was removed by solution, leaving the sponge in an almost white condition.

Following this permanganate treatment, a final bleaching with an acidified sodium bisulfite solution left the spongin in a permanently bleached state. Therefore, it was concluded that the oxidative permanganate treatment chemically decomposed the coloring matter in such a manner that it was incapable of being subsequently reformed.

Tablet Preparation

It was found that most of the materials making up the tablet formulas behaved in a very similar manner in that they offered no major compression problems. Special attention was required only when the spongin was added in excessive proportions and when it was added to the granulation just before compression.

When the spongin was added to the granulation prior to compression it would not flow uniformly with the granulation, but instead, it matted and bridged the die bore. Attempts to remedy this situation were unsuccessful. Lubrication with magnesium stearate was increased up to five per cent but did not alleviate the condition. Other lubricants, namely, boric acid, high molecular weight Carbowaxes and talc were also

tried with no success.

In the case of those tablets prepared containing spongin in proportions greater than ten per cent, satisfactory tablets were produced only when special handling of the formula was carried out. When preparing formulas containing 14 per cent spongin for preliminary study, great care was required in adding the binding agent during the granulation process. If an insufficient quantity was added, the resulting granulation had "spongy" characteristics. A granulation of this nature would not flow smoothly or uniformly into the dies regardless of the proportion of lubricant used; thus the final weight of the finished tablet was affected. On the other hand, if too great a quantity of binder was added, the granules resulting from the first screening would be excessively hard and resistant to further screening. It was necessary, therefore, to use the method of trial and error when determining the proportion of granulating agent required for optimum granulation. Since this proved to be impractical, this agent did not exceed a ten per cent concentration in any subsequent formula.

Table 7 summarizes the individual size characteristics of the tablet granulations prepared. It should be noted that with certain formulas comparatively large variations occurred in the granulations; however, in most cases this had no noticeable influence on tablet compression.

The granulations having magnesium hydroxide as the active ingredient were excessively soft and could be powdered when rubbed between the fingers. When compressing these magnesium hydroxide granulations high pressures were required in order to produce satisfactory tablets. If high

pressures were not used, capping of the tablets would result. When the tablets capped immediately following compression, the upper punch faces were observed to have the capped portion of the tablet adhered to them. However, some tablets were obtained in a whole state following compression and capped only when pressure was applied to the upper portion of the finished tablet with the thumb nail. This latter type of capping was most probably due to entrapped air in the tablet resulting from an excessive amount of fine powder in the granulation.

All other formulas prepared produced excellent, well defined, smooth tablets.

Disintegration Studies

The data listed in Table 9 indicate that the tablets prepared from formulas having powdered spongin as the disintegrating agent, disintegrated in all cases more quickly than the corresponding formulas having corn starch as the disintegrator. It should be noted that powdered spongin did not exceed five per cent of the tablet weight with the exception of those formulas prepared for preliminary study and two additional formulas used for purposes of comparison. On the other hand, corn starch was used in either 10 or 15 per cent concentrations.

All tablets containing powdered spongin disintegrated within the official requirements provided by the U. S. P. or N. F. Although tablets prepared from formula BSN-AT-5-b remained undisintegrated following three hours of testing, they offered no resistance to the gentle touch of a stirring rod following only five minutes of testing. When touched, the tablets readily broke into several small pieces which passed through the

No. 10 mesh screen of the basket-rack assembly in two or three minutes. Upon removal of these undisintegrated tablets from the disintegration apparatus after five minutes of testing, they were found to be extremely soft and easily crushed when squeezed between the fingers. Obviously, such a tablet when subjected to the peristaltic action of the G. I. tract would deliver the medication just as readily as one that would have fallen apart and passed through the screen. This tablet, therefore, would have been considered disintegrated in accordance with the new U. S. P. XV disintegration end-point.

In the preliminary studies conducted, all control tablets (those having no disintegrating agent added), with the exception of the soluble lactose tablets, showed no signs of disintegration subsequent to three hours testing. However, upon the addition of powdered spongin to the formulas, the same tablet formulas revealed no resistance to disintegration whatsoever. The data compiled also show that tablets prepared with 14 per cent spongin did not exhibit a substantial decrease in disintegration time over those tablets prepared with 7 per cent spongin. This indicates that large proportions of spongin are not required in order to accomplish satisfactory disintegration.

In general, synthetic sponge, when incorporated during the granulation process with the active ingredient and filler, possessed no advantage over lower concentrations of powdered spongin, but did surpass the disintegrating action of corn starch. However, when the synthetic sponge was granulated and added to the finished granulation prior to compression, it swelled within seconds and broke the tablet down into its original

granules very rapidly. Well defined, smooth tablets were obtained when adding the granulated synthetic sponge to the granulation prior to compression.

Since tablet hardness has an influence on the rate of disintegration, an attempt was made to maintain the tablet hardness within a range of 6.0 to 8.0 Kg. Four formulas, however, fell out of these limits. This was found to be caused either by the nature of the granulation being compressed or by difficulty encountered in adjusting the pressures to this hardness range.

The data listed in Table 10 and illustrated in Figures 4 and 5 indicate that the relationship which exists between the rate of tablet disintegration and tablet hardness depends on the tablet formula being tested. The results illustrated in Figure 4 show a minimum in the time-hardness curves for four tablet formulas containing powdered spongin as the disintegrant. In Figure 5, which represents the time-hardness relationship of three tablet formulas containing corn starch as the disintegrant, this minimum in the curve is completely absent. Instead, the disintegration rate varies directly with changes in hardness.

In general, a direct relationship manifests between disintegration time and tablet hardness; however, before assuming this to be true in any one case, a time-hardness curve should be plotted since in some instances faster rates of disintegration are obtained as the tablet hardness is increased. This continues up to an optimum hardness after which the ordinary relationship holds true.

Higuchi, Elowe, and Busse (54) have indicated a direct linear

dependency of hardness of tablets on the logarithm of the maximal compressional force. Since this is the case, curves similar those found in Figure 4 and Figure 5 would be obtained if compressional force was substituted for tablet hardness.

Berry and Ridout (30) determined the disintegration times of different tablets as a function of the ratio of the weight to height of the tablets which they called "compression ratio." Compression ratio is actually a measure of the maximal force applied during the compression of the tablets. They found that for some tablets there is a critical compression which will give a minimum time of disintegration.

The minima in curves representing a time-hardness relationship for the formulas (four) containing spongin are similar to those obtained by Berry and Ridout (30). Observations as to why this minima occurred with tablets containing spongin are also in correlation with those made by Berry and Ridout. It was found that the tablets showing this phenomenon disintegrated from the outside, that is, small pieces flaked off until the tablet was completely disintegrated. The disintegration of these tablets depends on the swelling of the sponge particles. Under a very light compression the tablets formed would be very soft and as a consequence have large intergranular spaces. Although the spongin swelled in these tablets, due to the large void spaces there was a certain lag period before the swelled particles began to exert pressure on the surrounding granules. This resulted in an inhibited disintegration rate. At the optimum hardness, however, as soon as the spongin particles swelled, they exerted sufficient pressure on the surrounding granules causing the tablets

to break apart more rapidly. When harder tablets were produced under heavier compressions, more time was required for the water to seep through the outer layers of the tablets and, as a result, slower disintegration rates were obtained.

It should be indicated that the minimum point on a time-hardness curve should not be used in determining the tablet hardness in actual production. It is necessary to run, in conjunction with these tests, friability tests. In many cases it will be found that this optimum hardness is merely a theoretical value and has no use in tablet manufacture since the tablets are far too friable at this point. On the other hand, if friability experiments show the tablets to be quite firm at this optimum hardness, it is obvious that this hardness should be utilized.

Friability Studies

The data compiled in Table 10 and illustrated in Figure 6 and Figure 7 indicate the relationship of tablet friability to tablet hardness. Although the friability values are pronounced for extremely soft tablets, they drop sharply as small changes in tablet hardness take place. Following the sudden drop in the friability value, little change is noted with progressively harder tablets.

In this investigation tablets having a friability value of 3.000 or less were considered as having a high degree of resistance to chipping or breaking.

As previously stated, in order to determine the optimum hardness for a particular tablet formula, it was necessary to conduct friability values on several series of tablets. This data was correlated with

disintegration time-hardness curves and the optimum tablet hardness for production was obtained.

Table 11 shows that when two 15-minute friability runs were made on the same tablets, the friability values after the second run averaged approximately 1.7 times those of the first run. From this it may be concluded that during the first shaking period, the tablet particles that were not firmly bonded were easily broken off. Therefore, upon being subjected to the second shaking period most of these loose particles were already removed leaving the more resistant structure of the tablet to be tested.

Upon inspection of the tablets subsequent to friability shaking tests, it was observed that the tablets chipped or broke from the outside leaving intact a more or less firm core. This type of breakage was noted for all tablet hardnesses, with the exception of those tablets that had completely broken up, and was most pronounced at hardnesses between 3.0 and 5.0 Kg. This indicates that when tablet granulations are being compressed at high pressures, the individual granules making up the finished tablet are not uniformly bound throughout the tablet. Instead, the granules in the center of the tablet are more strongly bound to one another than those granules making up the outer portion of the tablet.

It has been stated (58) that the compression process does not cause the granules to break down and intermesh with one another but merely tends to bond the granules by flattening them within the tablets. The individual granules, therefore, retain their identity in the finished tablet. When tablets were cut in a vertical plane, and examined with a

magnifying glass, it was noted that flattening of the granules was more pronounced in the center of the tablet than it was at the outer portion of the tablet. This, in addition to the type of breakage that takes place during friability shaking tests, indicates that under compression pressures, binding of the granules is greatest within the center of the tablet decreasing progressively in the outward direction.

Tablet structure may also be the basis for certain types of tablet disintegration. Some tablets are observed to disintegrate from the outside at a relatively fast rate, however, upon reaching a certain point this disintegration is slowed down considerably, and in some cases discontinued leaving a hard core in an undisintegrated condition. From the observations previously stated, it may be postulated that this type of disintegration in all probability is due to the varied degree of granule bonding throughout the tablet.

The results of data compiled in Table 12 indicate that the tablets protected with a cotton filler are retained in excellent condition after 15 minutes of shaking. Those tablets having friability values of 0.002, 0.003, and 0.006 showed no change in physical appearance when inspected by the naked eye.

In general, the results show that those tablets containing sponge as a disintegrating agent were no less friable than those containing corn starch as a disintegrator.

Binding and Lubrication Studies

Table 13 shows the comparative rate of disintegration of tablets prepared with different binding agents. Although insufficient data is

available, the information obtained reveals that the rate of disintegration is definitely influenced by the binding agent used in preparing the granulation. Starch paste and PVP solution were found to have approximately the same effect on disintegration. Zein solution was found to markedly inhibit the disintegration rate in two of the three formulas studied. This indicates that the influence of a binder on disintegration, besides being dependent on its adhesive properties, is also dependent on the materials being granulated. In general, syrup formed hard granules but had no adverse affect on disintegration.

Table 11 reflects the degree of firmness of tablets prepared with each of the four binders used. The results indicate that Zein solution formed the most resistant tablets while PVP solution, syrup, and starch paste in that order formed tablets of decreasing resistance.

The data listed in Table 14 and illustrated in Figure 8, Figure 9, and Figure 10 indicate that, with the exception of formula AH-AT-5, all unlubricated tablets tested disintegrated at a faster rate than those tablets that were lubricated. Two per cent lubricant based on the finished weight of the tablet was used in all formulas being compared. Boric acid, representing a soluble lubricant, had little influence on disintegration as compared with unlubricated tablets. It should be noted that boric acid was used for experimental purposes only and cannot be used in actual practice for tablets intended to be taken internally.

Magnesium stearate, although a very efficient lubricant, produced a severalfold increase in disintegration time. Magnesium stearate, when used as a lubricant, adheres to the granules and forms a thin water-impervious sheath around the tablet. Through the waterproofing action of this

sheath, the tablet is protected from the medium until this impervious layer is penetrated. This delay in absorption accounts for the several-fold increase in disintegration time. In one case using this agent, a tenfold increase was observed.

Talc, although insoluble, does not exhibit this waterproofing action on the finished tablet. Disintegration rates for the tablets lubricated with talc fell between those of boric acid and magnesium stearate. Talc possesses the disadvantage of giving the disintegration media a chalky white appearance.

In general, the results compiled indicate that the disintegration time of those formulas prepared with sponge as the disintegrating agent were not affected as greatly by changes in lubricating agent as were those formulas containing corn starch as the disintegrator.

Tables 31 and 32 show that, when comparing differently lubricated tablets following 500 hours of storage at varying conditions, only slight variation in changes of tablet weight between the different formulas occurred. Actually the only significant difference in weight change of the differently lubricated tablets was with those lubricated with magnesium stearate These tablets appeared to have absorbed less moisture than the other tablets when stored at humidities of 80 per cent and above. As revealed in Table 32, subsequent to storage at 95 per cent relative humidity for 500 hours, those tablets lubricated with magnesium stearate were found to retain their shape and were capable of being weighed. On the other hand, following these same storage conditions, the unlubricated tablets along with those lubricated with boric acid were found to be incapable

of retaining their shape when touched, and in addition had adhered in the container. Actually, the tablets in these latter two cases had absorbed excessive amounts of moisture which caused them to become "soggy" and "sticky" which in turn caused them to adhere in the container.

Storage Studies

The data collected subsequent to the storage of tablets in open containers at various temperature conditions are found in Tables 15, 21 and 25. The results indicate that disintegration time, hardness and weight changes following storage, vary considerably depending on the tablet formula in question. For example, formulas S-A-5, S-B-10 and AH-AT-5 all showed a significant increase in disintegration time when they were stored at 5° C., whereas formula AH-B-10 showed a decrease in disintegration time at the same temperature.

It was found that room temperature affected the disintegration time to some extent in all formulas. This was most likely due to the high relative humidities which prevailed during the storage period, at times being as high as 70 per cent.

As stated previously, disintegration time is usually directly related to changes in tablet hardness. Therefore, since increase in tablet hardness was shown to be generally dependent on the percentage of weight lost by the tablet during storage, it may be concluded that delayed disintegration times of tablets stored at 45° C. were caused by the pronounced moisture loss in the tablet.

The loss in weight revealed by formula S-B-10 was due to excessive moisture in the granulation. It should be noted that, as a result of this

moisture loss upon storage, significant changes in the hardness and disintegration time of these tablets occurred.

Tables 16, 22 and 26 show the effect of a closed container on tablets subjected to various temperature conditions. Little change in tablets was found following storage in this manner.

In general, the varied temperature conditions studied had a more pronounced influence on tablets containing spongin than they did on those tablets prepared with corn starch as the disintegrant.

The results listed in Tables 23, 27 and 29 show that storage in open containers at various relative humidities is of significant interest. Again, as stated previously, the deviations taking place in tablet hardness and disintegration time are shown to be closely related to the changes taking place in tablet weight.

At low relative humidities of 30 and 40 per cent little change is observed in tablet weight. Likewise, changes taking place in tablet hardness and disintegration are also small. As the humidities begin to reach higher levels, however, changes in these three properties begin to become significant. At 50 per cent relative humidity, increase in tablet weight, although slight, is definitely noticeable. At this same humidity tablet hardness began to show decreases of from 0.5 to 1.0 Kg. In addition, signs of increased disintegration time were noted in all cases.

Following storage at 80 per cent relative humidity, a much greater increase in tablet weight took place, and as would be expected the tablets were much softer. The disintegration time also showed a marked increase for all tablet formulas.

Relative humidities of 95 per cent caused the tablets to become soggy, swollen, and in many cases moldy. Attempts to test these tablets were unsuccessful since the tablets would not retain their shape when touched.

Tables 24, 28 and 30 indicate that tablets stored in closed containers at various relative humidities show no significant changes in weight, hardness, or disintegration time following storage.

In general, it may be stated that tablet formulas prepared using powdered spongin as the disintegrating agent are more susceptible to increases in relative humidities than those tablets containing corn starch as the disintegrant. These results are in accord with those found in Table 8 and illustrated in Figure 3. Here, the data compiled indicate that powdered spongin has a greater capacity for absorbing moisture than corn starch.

SUMMARY

The value of sponge, both natural and synthetic, as a disintegrating agent in compressed tablets was investigated.

In addition, a method for cleansing, bleaching and grinding the natural sponge prior to its incorporation in tablet formulas has been devised.

Tablets prepared using sponge as the disintegrating agent proved to disintegrate more rapidly than those prepared with corn starch as the disintegrant. The disintegration time for tablets containing spongin, when related to tablet hardness, was characterized by a minimum in the curve which took place at an optimum hardness. Tablets prepared with corn starch, however, failed to show this phenomenon. Instead, they usually revealed a linear relationship.

Synthetic sponge, when granulated with starch paste and added to the finished granulation prior to compression, was found to be very efficient as a disintegrant. This agent swelled immediately upon contact with water and broke down the tablet into its original granules which in turn rapidly disintegrated.

Shaking tests indicated that sponge had no adverse affect on the friability of the finished tablet. Using these friability tests as a basis, it was concluded that the degree of granule bonding throughout a tablet is varied. Apparently, the granules are bonded more firmly within the center of the tablets with the magnitude of this bonding decreasing

in an outward direction.

Lubrication studies revealed magnesium stearate to have a marked influence on the disintegration time of tablets. In most instances, when tablets were lubricated with magnesium stearate, a severalfold increase over unlubricated tablets was observed. This influence on disintegration was more pronounced in tablets prepared with corn starch as the disintegrant.

Storage studies indicated that tablets prepared with sponge, and stored under specified conditions, were, in general, less stable in the properties studied than those tablets containing corn starch.

BIBLIOGRAPHY

1. Helenore, J. C., Chain Store Age, Drug Executives Edition, 29, 93 (1953).

2. White, R. C., J. Am. Pharm. Assoc., 9, 788 (1920).

3. Gross, H. G., and Becker, C. H., J. Am. Pharm. Assoc., Sci. Ed., 41, 157 (1952).

4. Caspari, C., and Kelly, E. F., "A Treatise on Pharmacy", Lea and Febiger, Philadelphia, Pa., 1939, p. 408.

5. Little, A., and Mitchell, K. A., "Tablet Making", Northern Publishing Company, Ltd., Liverpool, England, 1949, p. 12.

6. Peck, W. C., Pharm. J., 143, 171 (1939).

7. "Research in Tablet Making", Pharm. J., 150, 184 (1943).

8. Burlinson, H., J. Pharm. and Pharmacol., 6, 1055 (1954).

9. Villacorta, C. V., Thesis, "Studies of Compressed Tablet Manufacture," University of Illinois, 1950.

10. Chavkin, L., Drug and Cosmetic Ind., 75, 466 (1954).

11. Silver, J. A., and Clarkson, R., "Manufacture of Compressed Tablets", F. J. Stokes Machine Company, Philadelphia, Pa., 1947, p. 19.

12. Kebler, L. F., J. Am. Pharm. Assoc., 3, 820 (1914).

13. Letters in Chemist and Druggist, 37, 531, 563, 603, 665, 695 (1890).

14. Dieterich, E., Pharm. Ztg., 35, 400 (1890).

15. Blaschnek, R., Pharm. Post, 42, 169 (1909); through Pharm. Ztg., 54, 178 (1909).

16. Kebler, L. F., J. Am. Pharm. Assoc., 3, 937 (1914).

17. Husa, W. J., Drug Markets, 20, 317 (1927).

18. White, E., and Robinson, R. A., Year-Book of Pharm., p. 417 (1902).

19. White, E., and Rodwell, H., Ibid., p. 487 (1903).

20. Lowry, W. J., Proc. Am. Pharm. Assoc., 54, 663 (1906).

21. Dunnet, P., Chemist and Druggist, 78, 206 (1911).

22. White, R. C., J. Am. Pharm. Assoc., 11, 345 (1922).

23. Husa, W. J., Ibid., 17, 38 (1928).

24. "Tablet Making", Pharm. J., 126, 233 (1931).

25. Davis, H., and Gillett, F. H., Ibid., 133, 503 (1934).

26. Sprengler, H., and Schenker, E., Pharm. Acta Helv., 12, 339 (1937).

27. Brown, C. L. M., Quart. J. Pharm. and Pharmacol., 12, 489 (1939).

28. Sprengler, H., and Jud, J., Pharm. Acta Helv., 18, 565 (1943).

29. Burlinson, H., and Pickering, C., J. Pharm. and Pharmacol., 2, 63 (1950).

30. Berry, H., and Ridout, C. W., Ibid., p. 619.

31. Holstius, E. A., and DeKay, H. G., J. Am. Pharm. Assoc., Sci. Ed., 41, 505 (1952).

32. Milne, G. R., Chemist and Druggist, 139, 276 (1943).

33. Granberg, C. B., and Benton, B. E., J. Am. Pharm. Assoc., Sci. Ed., 38, 648 (1949).

34. Swintosky, J., and Kennon, L., Ibid., 42, 505 (1953).

35. Firouzabadian, H., and Huyck, L. C., Ibid., 43, 248 (1954).

36. Eatherton, L. E., et al., Drug Standards, 23, 42 (1955).

37. Swintosky, J., et al., J. Am. Pharm. Assoc., Sci. Ed., 44, 112 (1955).

38. Curlin, L., Ibid., p. 16.

39. Evanson, R. V., and DeKay, G. H., Bull. Natl. Formulary Comm., 18, 45 (1950).

40. Ewe, G. E., Proc. Am. Pharm. Mfrs'. Assoc., p. 75 (1930).

41. Howard, B. F., Quart. J. Pharm. and Pharmacol., 9, 528 (1936).

42. Berry, H., Ibid., 12, 501 (1939).

43. Berry, H., and Smith, A. N., Ibid., 17, 248 (1944).

44. Malpass, G. N., Am. J. Pharm., 114, 167 (1942).

45. Calamari, J. A., and Roth, P. B., Proc. Am. Pharm. Mfrs'. Assoc., p. 75 (1942).

46. Hoehn, W. M., Bull. Natl. Formulary Comm., 13, 162 (1945).

47. Smith, A. N., Pharm. J., 156, 317 (1946).

48. "Science Papers", Pharm. J., 157, 86 (1946).

49. Gershberg, S., and Stoll, F., J. Am. Pharm. Assoc., Sci. Ed., 35, 284 (1946).

50. "United States Pharmacopeia, Fourteenth Revision", Mack Publishing Company, Easton, Pa., 1950, p. 700.

51. Ibid., "Fifteenth Revision", 1955, p. 937.

52. Higuchi, T., et al., J. Am. Pharm. Assoc., Sci. Ed., 41, 93 (1952).

53. Holstius, E. A., and DeKay, H. G., Ibid., p. 505.

54. Higuchi, T., et al., Ibid., 43, 685 (1954).

55. Levi, R. S., Thesis, "A Comparative Study of Binding Agents for Compressed Tablets", University of Florida, 1951.

56. Sperandio, G. J., and DeKay, H. G., J. Am. Pharm. Assoc., Pract. Ed., 10, 572 (1949).

57. Griffin, J. C., and Huyck, C. L., Ibid., Sci. Ed., 44, 251 (1955).

58. Strickland, W. A., et al., Ibid., 45, 51 (1956).

59. Wolff, J. E., Ibid., 36, 407 (1947).

60. Smilek, M., et al., Drug Standards, 23, 87 (1955).

61. Münzel, von K., and Kägi, W., Pharm. Acta Helv., 29, 53 (1954).

62. Beeler, E. C., and Gathercoal, E. N., J. Am. Pharm. Assoc., Sci. Ed., 30, 56 (1941).

63. Raff, A. M., Ibid., 44, 290 (1955).

64. Ewe, G. E., Ibid., 23, 1205 (1934).

65. Leonard, C. S., Proc. Am. Pharm. Mfrs'. Assoc., p. 20 (1932).

66. Silver, J. A., and Clarkson, R., Ibid., p. 105 (1933).

67. Tschirch, A., Schweiz. Apoth. Ztg., 77, 85 (1939); through Chem. Abstracts, 34, 2536 (1940).

68. Wood, H. C., et al., "The Dispensatory of the United States", J. B. Lippincott Co., Philadelphia, Pa., 18th edition, 1899, p. 1799.

69. Oficjalski, P., Pharm. Zentralhalle, 78, 174 (1937).

70. deLaubenfels, M. W., "Papers from the Tortugas Laboratory", 30, published by the Carnegie Institute of Washington, March, 1936.

71. Städeler, G., Ann. Chem. u. Pharm., 111, 12 (1859).

72. Schmidt, C. L. A., "The Chemistry of Amino Acids and Proteins", Charles C. Thomas, Springfield, Illinois, 2nd edition, 1944, p. 278.

73. Block, R. J., and Bolling, D., J. Biol. Chem., 127, 685 (1939).

74. Ramsey, J. C., Thesis, "An Elemental Analysis of Some Florida Salt Water Sponges", University of Florida, 1948, p. 18.

75. Clancy, V. J., Biochem. J., 20, 1186 (1926).

76. Smith, J. G., J. Ind. Eng. Chem., 5, 850 (1913).

77. Wintter, J. E., Thesis, "Amino Acids From the Florida Wool Sponge", University of Florida, 1950, p. 6.

78. Gross, H. G., Thesis, "A Comparative Study of Tablet Disintegrating Agents", University of Florida, 1951, p. 21.

79. Husa, W. J., "Pharmaceutical Dispensing", 4th edition, Husa Brothers, Iowa City, Iowa, 1951, p. 109.

80. "Why Glycerine for Drugs and Cosmetics?", Glycerine Producers' Assoc., New York, N. Y., p. 13.

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This dissertation was prepared under the direction of the chairman of the candidate's supervisory committee and has been approved by all members of the committee. It was submitted to the Dean of the College of Pharmacy and to the Graduate Council and was approved as partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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